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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Original Communications

Ten Years' Experience With Bleeding Peptic Ulcer With Emphasis on Forty-Five Fatal Cases. Nathan Shapiro, M.D., M.S., and Leon Schiff, M.D., Ph.D., Cincinnati, Ohio ---- 327

Surgical Intervention in Massive Gastroduodenal Bleeding. Frederick H. Amendola, M.D., New York, N. Y. ---- 340

The Role of Trypsin in the Pathogenesis of Acute Hemorrhagic Pancreatitis and the Effect of an Antitryptic Agent in Treatment. Benjamin Rush, Jr., M.D., and Eugene E. Cliffton, M.D., New Haven, Conn. ---- 349

Effect of Simultaneous Oral Administration of Aureomycin and Aluminum Hydroxide Gel on Fecal Urobilinogen. William D. Hayford, M.D., and Burton A. Waisbren, M.D., Minneapolis, Minn. ---- 361

The Prophylactic Use of Terramycin in Experimental Clostridium Welchii Infection in Guinea Pigs. William R. Sandusky, M.D., Constance F. Keeble, B.S., William P. Wharton, M.D., and Richard N. Taylor, M.D., Charlottesville, Va. ---- 365

Fibrotic Stenosis of the Terminal Common Duct. Philip F. Partington, M.D., Cleveland, Ohio ---- 367

(Contents continued on inside back cover)

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SURGERY

VOL. 31 MARCH, 1952 NO. 3

Original Communications

TEN YEARS' EXPERIENCE WITH BLEEDING PEPTIC ULCER WITH EMPHASIS ON FORTY-FIVE FATAL CASES

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INTRODUCTION

FOLLOWING a visit to Professor Meulengracht's Clinic, one of us (L. S.) became impressed with the value of the prompt feeding program and instituted it in the Cincinnati General Hospital on Oct. 1, 1937. A definite decrease in mortality occurred. Since it has become apparent that prompt feeding is not the final solution to the management of bleeding peptic ulcer, it was decided to study our material with particular attention to the fatal cases. The purpose of this study was to gather data which would prove helpful in prognosis and management. Accordingly, cases admitted to the medical and surgical services of the Cincinnati General Hospital during a ten-year period extending from Oct. 1, 1937, to Sept. 30, 1947, were selected for this study. During this period 510 patients (640 admissions*) entered the Cincinnati General Hospital with acute gastrointestinal hemorrhage. Two hundred fifty-nine of these patients (339 admissions) had bleeding peptic ulcer and forty-five of them died. Forty of the forty-five fatal cases came either to operation or to autopsy.

Age.—Fig. 1 shows the age distribution of the 45 fatal and 294 nonfatal cases of bleeding peptic ulcer. It demonstrates, as is well known, that death may result from bleeding even in the third and fourth decades of life, although it is much more likely to do so later.[1-3] It also illustrates that duodenal ulcer is more frequent in the younger age groups, while gastric ulcer is relatively more frequent in older patients. The over-all mortality rate was 13 per cent, being 4 per cent in patients under forty years of age and 19 per cent in those over forty.

Sex.—There were 40 men and 5 women among the fatal cases (Table I). The mortality among the men was 14 per cent and among the women 9 per cent.

This study was aided by a grant from the Committee on Peptic Ulcer of the American Gastroenterological Association through the United States Public Health Service.

Received for publication, July 16, 1951.

*Hereafter each admission is considered a separate case.

These figures suggest that fatal hemorrhage occurs with slightly increased frequency in men. This has been recorded by Lewison[1] but has not been the experience of Avery Jones.[4]

TABLE I. SEX, COLOR, AND MORTALITY
(339 CASES OF BLEEDING PEPTIC ULCER)

	TOTAL CASES	FATAL CASES	MORTALITY (PER CENT)
Sex			
Male	286	40	14
Female	53	5	9
Color			
White	228	33	14
Black	110	12	11
Other	1	0	0

Color.—There were 33 white and 12 Negro patients in the fatal group with respective mortality rates of 14 per cent and 11 per cent (Table I).

Duration of Ulcer Symptoms.—Table II lists the duration of ulcer symptoms prior to fatal hemorrhage. The duration of symptoms was unknown in 6 of the 45 patients. Five of the six were admitted in an unconscious state from which they never recovered, and one was suffering with mental disease. Of the remaining 39, 5 had had no ulcer symptoms preceding the hemorrhage, 17 had had symptoms for less than 3 years, while 17 had had symptoms for longer periods. This suggests that the duration of symptoms prior to the onset of hemorrhage is not a determining factor in prognosis as has been noted by others.[5, 6]

TABLE II. DURATION OF ULCER SYMPTOMS PRIOR TO FATAL HEMORRHAGE
(45 CASES)

PERIOD OF TIME	NUMBER OF CASES
No symptoms	5
2 weeks or less	4
2 weeks to 3 months	3
3 to 12 months	1
1 to 3 years	9
3 to 5 years	4
5 to 10 years	4
10 to 20 years	6
"Several years"	3
Unknown	6

Previous Hemorrhage.—Thirty-three patients succumbed during the first hemorrhage and 8 died following a second episode of bleeding. The over-all mortality rate in the initial hemorrhage was 14 per cent and that in the second hemorrhage was 13 per cent. There were 45 cases with more than 2 hemorrhages and no deaths (Table III). This suggests that the first and second hemorrhages are the most serious, a circumstance which has been emphasized by others.[7, 8]

Minimum Hemoglobin and Red Blood Cell Values.—Fig. 2 illustrates the correlation between mortality and minimum hemoglobin and red blood cell values. When the hemoglobin was less than 4 Gm. per cent the mortality rate

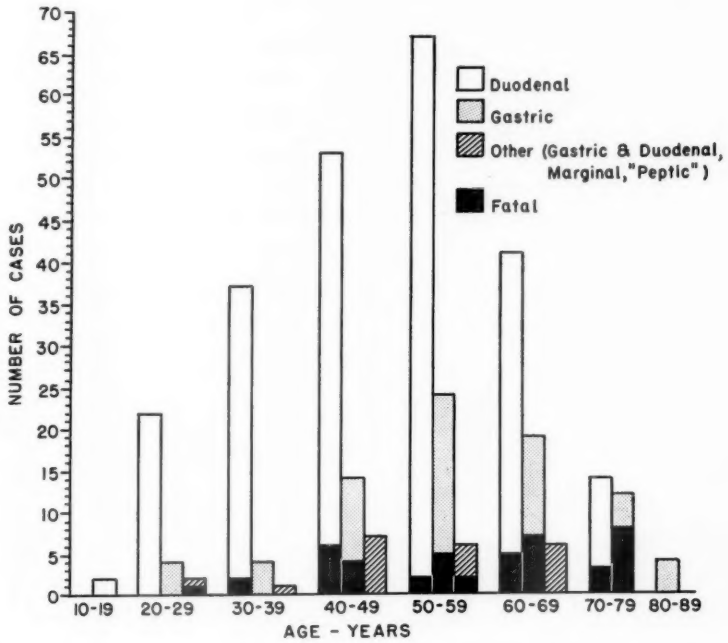

Fig. 1.—Age distribution and ulcer site (339 cases of bleeding peptic ulcer).

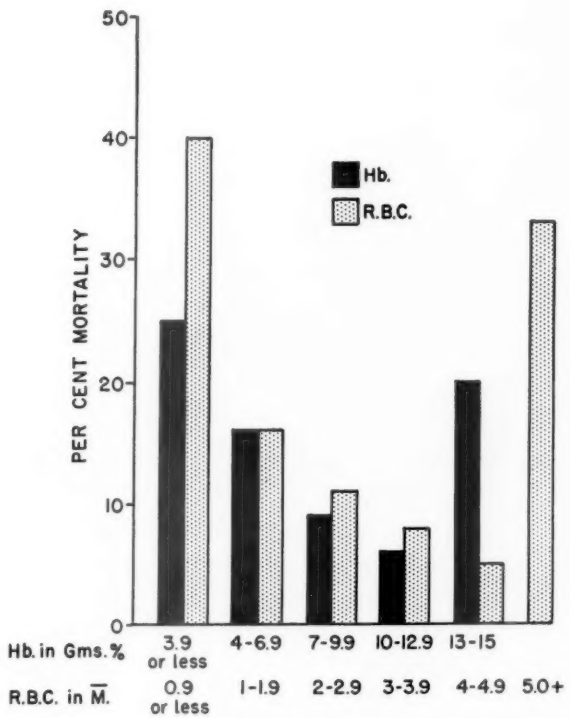

Fig. 2.—Correlation of hemoglobin and red blood count values and mortality, 334 cases of bleeding peptic ulcer (five cases had neither hemoglobin nor red blood count).

was 25 per cent. There was a fairly rapid drop in the mortality as the hemoglobin concentration increased. Similarly when the red blood cell count was less than 1 million the mortality was 40 per cent and dropped precipitously with rising red blood cell values. The large number of fatalities among patients with normal hemoglobin and red blood cell values occurred in those in whom the bleeding was complicated by perforation or serious systemic disease.

TABLE III. MORTALITY AND PREVIOUS EPISODES OF HEMORRHAGE (339 CASES OF BLEEDING PEPTIC ULCER)

NUMBER OF PREVIOUS HEMORRHAGES	TOTAL CASES	FATAL CASES	MORTALITY (PER CENT)
None	230	33	14
1	60	8	13
2	23	0	–
3	10	0	–
4	6	0	–
5 or more	6	0	–
Unknown	4	4	100

Site of Ulcer.—Table IV reveals a preponderance of gastric ulcers in the 45 fatal cases in contrast to a 4:1 ratio of duodenal to gastric ulcer in the nonfatal group. This indicates that hemorrhage from gastric ulcer offers a more serious prognosis than bleeding duodenal ulcer. This has been emphasized by others.[2, 6, 7] Table V demonstrates that, in our experience, bleeding gastric ulcer has been fatal with approximately 4 times the frequency of duodenal ulcer.

TABLE IV. LOCATION OF ULCER (339 CASES OF BLEEDING PEPTIC ULCER)

	FATAL CASES	NONFATAL CASES
Gastric	24	57
Duodenal	18	218
Gastric and duodenal	2	7
Marginal	0	8
"Peptic"	1	4

TABLE V. COMPARATIVE MORTALITY IN BLEEDING GASTRIC AND DUODENAL ULCER

ULCER SITE	NUMBER OF CASES	NUMBER OF FATAL CASES	MORTALITY RATE (PER CENT)
Gastric	81	24	30
Duodenal	236	18	8

There seems little reason to doubt that gastric ulcers bleed more copiously than duodenal ulcers. Fig. 3 demonstrates the red blood cell and hemoglobin values in patients with duodenal and gastric ulcers. There is a tendency for lower levels to occur in association with bleeding gastric ulcers of both the fatal and nonfatal varieties. In parallel manner, shock occurred in 33 per cent of the nonfatal cases of gastric ulcer compared with an incidence of 20 per cent among those with duodenal ulcers. Baker[9] and Welch[7] attribute the more severe bleeding in gastric ulcer to erosion of the main trunks of the right or left gastric arteries as compared with erosion of the branches of the gastroduodenal or the pancreaticoduodenal arteries by duodenal ulcers.

Hematemesis and Melena.—Table VI illustrates the relative frequency of hematemesis and melena in 43 fatal cases in which such data were obtainable. In 24 of these patients hematemesis preceded the melena and in 10 it followed melena. There was thus a total of 34 patients with hematemesis and 9 with only melena. Therefore, among the fatal cases, hematemesis either preceded or followed by melena, occurred approximately 4 times as often as melena alone. This would tend to substantiate the observations of Meulengracht[6] and Pedersen[3] who claim that hematemesis is of graver significance than melena alone. However, other data obtained in the nonfatal cases militate against this conclusion. Table VI indicates the frequency of hematemesis, either preceded or followed by melena, as compared with the occurrence of melena alone to be the same as in the fatal cases, i.e., about 4 to 1. There would thus seem to be little reason to accept hematemesis as a more serious prognostic symptom than melena alone.

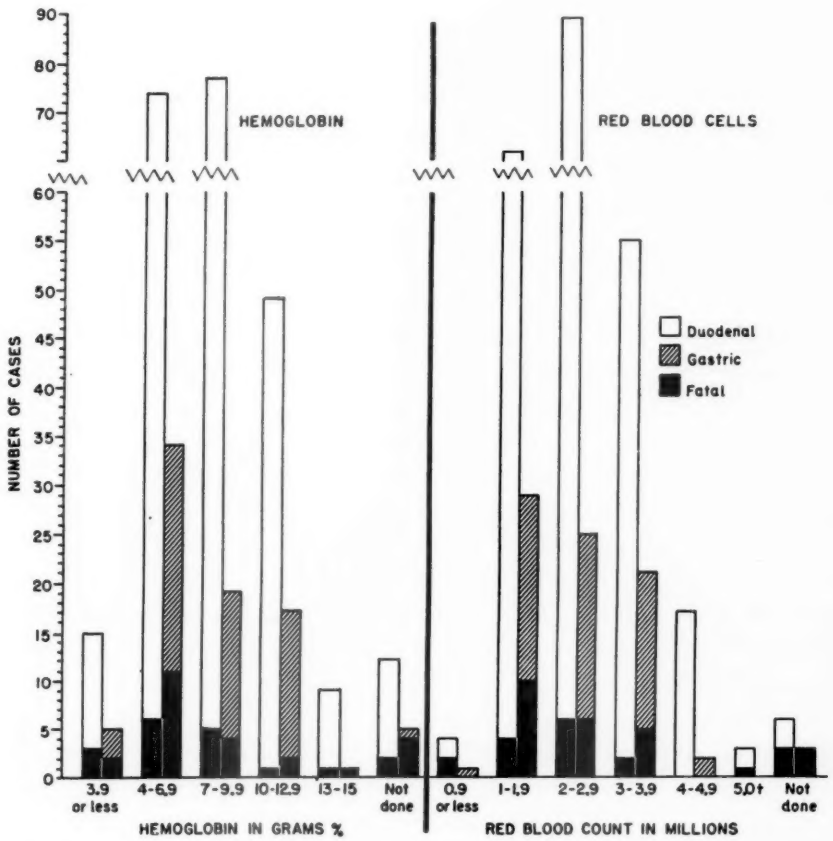

Fig. 3.—Minimum hemoglobin and red blood count values in bleeding peptic ulcer (236 duodenal and 81 gastric).

Recurrent and Continuous Hemorrhage.—While it is admittedly difficult to determine whether hemorrhage is recurrent or continuous, we have, nevertheless, attempted this distinction and find that in 21 of the 45 cases hemorrhage was probably recurrent while in 24 patients it was continuous. This would bear

out Meulengracht's experience that recurrent and continuous hemorrhage have equally serious implications.[6]

TABLE VI. INCIDENCE OF HEMATEMESIS AND MELENA
(339 CASES OF BLEEDING PEPTIC ULCER)

	NUMBER OF CASES	PER CENT OF CASES
Fatal Cases		
Hematemesis	24	79
Melena preceding hematemesis	10	
Melena only	9	21
Unknown	2	
Nonfatal Cases		
Hematemesis	161	78
Melena preceding hematemesis	67	
Melena only	66	22

Cause of Death.—Fourteen of the 45 patients died of exsanguination. Twelve additional patients were operated upon in an attempt to arrest the acute hemorrhage but died postoperatively making a total of 26 who probably would have bled to death. There were 7 patients with complications additional to the bleeding, and lastly, there were 12 cases in whom the bleeding ulcer complicated serious systemic disease.

In Tables VII through X are listed all the fatal cases arranged in groups. The first 5 patients shown in Table VII died within 24 hours after reaching the hospital. Two patients died in the receiving ward before any form of therapy could be instituted. Three others were not hospitalized long enough to establish a diagnosis prior to death. The next 9 patients listed in Table VII died of exsanguination, but lived for a longer period than the first 5. It is to be noted that all of these 9 bled profusely and many suffered from shock. Utilizing our present criteria for operation, probably 8 of these 9 patients would have been explored. How many of these might have been salvaged is impossible to say.

Table VIII lists the 12 patients who were subjected to emergency surgery but who died following operation. Under present-day management 3 of these (Nos. 153, 180, 588) would have been explored much earlier. There were 5 patients over 60 years of age in whom cardiovascular or pulmonary complications contributed to the fatal outcome. Prompt digitalization or antibiotic therapy, had it been available, might have prevented these deaths.

Table IX demonstrates 7 fatal cases in which complications developed or in which the bleeding represented an additional manifestation. Five of these patients had perforations, 3 of them bleeding relatively mildly. Two patients developed pneumonia and died after the bleeding had apparently ceased and the red blood cell count was rising.

Finally, the occasional patient should be mentioned who, for one reason or another, is mistakenly considered to have a malignant lesion (Table VIII, No. 385, Table IX, Nos. 469, 569) and whose treatment may be less energetic for this reason.

Table X tabulates the fatal cases with coexistent systemic disease. In most instances the systemic disorder overshadowed the bleeding ulcer. The minimum

red cell levels were higher than the average values among the other fatal cases suggesting that the bleeding was only a contributing factor to the fatal outcome. Indeed, associated systemic disease was usually of sufficient severity to represent the lethal process.

TABLE VII. DEATH DUE TO EXSANGUINATION

SERIES NO.	NAME	AGE	COLOR	SEX	DIAGNOSIS	DATE OF ADMISSION	ONSET OF HEM.	DATE OF DEATH	MIN. R.B.C. (MILLIONS)	MIN. HB. (GM. %)	AUTOPSY
70	G. L.	44	W	M	Duod. ulcer, chron.	3/ 3/39	3/ 1	3/ 3	1.01	1.0	+
399	L. S.	62	W	M	Gast. ulcer, chron.	5/ 4/44	5/ 2	5/ 5	1.5	5.5	+
441	M. T.	47	C	F	Duod. ulcer	12/29/44	12/23	12/29	No data	No data	–
494	W. H.	47	W	M	Duod. ulcer, chron.	10/21/45	10/18	10/21	No data	No data	–
572	J. S.	79	W	M	Gast. ulcer, chron.	11/ 9/46	?	11/10	3.77	5.0	+
2	L. R.	69	W	M	Duod. ulcer, chron.	4/23/38	4/17	4/25	1.54	7.8	+
6	C. S.	56	W	M	Duod. ulcer, chron.	1/23/38	1/20	1/28	0.98	4.0	+
85	C. B.	77	W	M	Gast. ulcers, chron.	8/19/39	8/17	8/23	1.92	6.2	+
291	H. S.	28	W	M	Gast. & duod. ulcer	5/ 4/39	5/ 4	5/ 8	2.21	8.0	–
309	C. F.	49	W	M	Gast. ulcer, subacute	1/ 7/43	1/ 5	1/14	1.8	4.0	+
338	F. F.	50	W	M	Duod. ulcer, chron.	6/10/43	6/ 7	6/15	1.16	5.0	+
385	J. C.	79	C	M	Duod. ulcer, chron.	2/17/44	2/ 1	2/24	2.27	3.0	+
476	B. M.	50	C	M	"Peptic" ulcer	7/ 7/45	2 to 3 hr. before adm.	7/ 9	1.1	4.0	–
492	J. J.	47	C	M	Gast. ulcer, chron.	9/27/45	9/20	10/ 2	1.1	4.0	+

DISCUSSION

During the period of this study, the prompt feeding program was in use.

As we reviewed the records of the fatal cases, two errors in management were noted. One was the sparing use of blood transfusions in a number of our cases. This was due in part to the fact that we did not have a blood bank until the study had been underway for more than 2 years. At the present time, we

TABLE VIII. CASES SUBJECTED TO SURGERY FOR ACUTE BLEEDING WITH DEATH FOLLOWING OPERATION

SERIES NO.	NAME	AGE	COLOR	SEX	DIAGNOSIS	DATE OF ADMISSION	ONSET OF HEM.	DATE OF OPERATION	DAY OF DEATH AFTER ONSET OF HEM.	MIN. R.B.C. (MILLIONS)	MIN. HB. (GM. %)	AUTOPSY	COMMENT
80	E. H.	60	C	M	Duod. ulcer, chron.	8/23/39	12 hr. before adm.	8/24	2nd	3.4	10.0	–	In almost constant shock, died on operating table
136	L. W.	69	W	M	Duod. ulcer, chron.	4/21/40	4/30	5/ 2	6th	2.04	7.4	+	Atelectasis, pneumonia, auric. fibrillation
153	J. R.	42	C	M	Duod. ulcer, chron.	7/17/40	7/16	7/18	2nd	2.68	6.5	+	Operated during third episode of shock; died on operating table
174	T. B.	61	W	F	Gast. ulcer, chron.	11/24/40	12 hr. before adm.	11/25	22nd	2.08	6.5	+	Atelectasis, pneumonia, wound disruption
180	D. C.	39	C	M	Duod. ulcer, chron.	12/24/40	12/ 3	12/31	28th	0.89	3.6	–	Bordered on shock all day before surg.; died on operating table
429	C. L.	54	W	M	Gast. ulcer, chron.	10/30/44	10/25	11/1	10th	1.15	4.0	+	Local excision of ulcer because of critical condition; hemorrhage recurred postoperatively; pneumonia
469	J. K.	67	W	M	Gast. ulcer, chron.	5/25/45	4 hr. before adm.	6/12	20th	2.8	7.5	+	Ca. of pancreas suspected at operation, & surg. discontinued

493	J. D.	67	W	M	Gast. ulcer, chron.	10/17/45	9/29	10/21	30th	1.4	2.5	+	Postoperative atelectasis, pneumonia, & congestive failure
514	M. P.	60	W	F	Duod. ulcer, chron.	1/ 7/46	1/ 3	1/17	14th	2.45	7.0	+	Recurrent episodes of hemorrhage and shock; refused to permit surgery until 10 days after admission when condition extremely poor
560	H. S.	75	W	M	Gast. ulcer, chron.	8/27/46	8/26	8/31	5th	1.13	3.0	+	Exploration failed to reveal source of bleeding; autopsy disclosed 2 rather shallow chron. ulcers on lesser curvature of fundus
569	T. S.	78	W	M	Gast. ulcer, chron.	11/ 1/46	11/ 1	11/ 3	2nd	2.04	6.5	–	Exploration revealed huge indurated gast. lesion fixed to retroperitoneal tissues and thought to be ca.; total gastrectomy not feasible; control of bleeding unsuccessful
588	W. P.	69	W	M	Gast. ulcer, chron.	1/16/47	1 mo. before adm.	1/19	46th	1.60	4.0	–	3 episodes of shock; exploration under local anesthesia because of poor cond.; large gast. ulcer with pulsating vessel in base; vessels ligated; developed congestive failure, pulm. edema, pneumonia; also further bleeding

TABLE IX. FATAL CASES WITH COMPLICATIONS

SERIES NO.	NAME	AGE	COLOR	SEX	DIAGNOSIS	DATE OF ADMISSION	ONSET OF HEM.	DAY OF DEATH AFTER ONSET OF HEM.	MIN. R.B.C. (MILLIONS)	MIN. HB. (GM. %)	AUTOPSY	COMMENT
101	J. S.	48	W	F	Gast. ulcer, chron.	11/26/39	11/18	11th	1.67	4.2	+	Perforation 48 hr. after adm. for hemorrhage; died after repair
301	C. D.	34	C	M	Duod. ulcer, chron.	10/31/42	12/19	2nd	No data	7.5	+	Adm. for perforated duod. ulcer, peritonitis, subphrenic abscess, intest. obst., fecal fistula; melena 48 hr. before death
320	H. M.	59	W	F	Gast. ulcers, mult. acute; chron. duod. ulcer	2/19/43	2/19	5 hr.	4.15	12.0	+	Mental dis.; no hist.; chron. duod. ulcer, perforated, with peritonitis, abscess formation
331	W. M.	58	C	M	Gast. ulcer, chron.	5/ 9/43	5/ 7	24th	1.18	5.5	+	Recurrent bleeding; x-ray diag. of gast. ca.; developed pneumonia when Hb. & R.B.C. were rising
464	H. P.	74	W	F	Duod. ulcer, chron.	5/ 4/45	4/30	12th	2.78	5.5	–	Hb. & R.B.C. rising when pneumonia supervened
506	J. B.	42	W	M	Duod. ulcer, chron.	6/25/44	6/21	5th	5.8	17.0	+	Asthma, emphysema, inactive pulmonary tuberculosis; tarry stools 4 days; perforated 4 hr. before adm.; condition too poor for surg.
523	M. R.	67	W	F	Gast. ulcer, chron.	2/27/46	2/20	10th	No data	12.5	+	Perforation prob. 2 weeks prior to adm.; melena few days before, adm. in moribund state

TABLE X. FATAL CASES ASSOCIATED WITH SYSTEMIC DISEASE

SERIES NO.	NAME	AGE	COLOR	SEX	DIAGNOSIS	DATE OF ADMISSION	ONSET OF HEM.	DAY OF DEATH AFTER ONSET OF HEM.	MIN. R.B.C. (MILLIONS)	MIN. HB. (GM. %)	AUTOPSY	ASSOCIATED SYSTEMIC DISEASE	COMMENT
194	J. H.	62	W	M	Duod. ulcer, chron.	3/14/41	3/13 (?)	1st	3.04	7.8	+	Recent skull fracture	
199	J. H.	71	W	M	Duod. ulcer, chron.	3/28/41	3/31	11th	1.8	4.0	+	Hepatic cirrhosis	
288	O. C.	45	W	M	Duod. ulcer, chron.	5/15/38	5/7	17th	2.0	4.4	+	Urinary extravasation with cellulitis	
294	R. G.	76	W	F	Gast. ulcer, acute	9/ 2/40	9/22	2nd	No data	No data	+	Disseminated, hematogenous miliary tuberculosis	
296	W. B.	53	C	M	Gast. ulcers, mult.; 1 chron.	10/31/41	11/29	5th	3.49	No data	+	Widespread periarteritis nodosa	Bleeding contributed insignificantly to death
306	M. C.	40	C	F	Gast. ulcer, subacute or chron.	12/26/42	12/12	17th	2.0	No data	+	Malig. hypertension with uremia	
353	J. B.	54	W	M	Gast. ulcer, subacute	6/24/41	5/10/43	3rd	3.0	7.0	+	Osseous tuberculosis	
370	W. B.	69	W	M	Gast. ulcer, chron.	12/ 6/43	12/7	2nd	2.45	10.0	+	Hepatic cirrhosis	Adm. in unconscious state
396	M. S.	59	W	M	Gast. ulcers, mult. acute & 1 subacute	4/30/44	5/2	2nd	3.72	13.0	+	Myocard. infarc.; hepatic cirrhosis	Melena 24 hr. before death
442	L. G.	71	W	F	Gast. ulcer, chron.	1/ 4/45	1/17	3rd	2.67	7.0	+ (limited to abdomen)	Arteriosclerotic heart dis. with congestive failure	
458	W. S.	73	C	M	Gast. ulcers, mult. acute & subacute	3/31/45	4/4	2nd	3.2	7.0	+	Bronchogenic ca. with metastases	
509	P. W.	70	W	M	Gast. ulcer, acute	2/ 3/45	2/8	2nd	No data	No data	+	Acute & old myocardial infarction; thrombosis of pulm. art.	About 36 hr. before death, evid. of G.I. bleeding; acute gast. ulcer with hemorrhagic gastritis which contributed little to death

use either a constant drip transfusion after the method of Marriott and Keckwick[10] or repeated transfusions until the hematocrit and blood count are approximately 90 per cent of the estimated normal level. By this means shock may be prevented in patients with recurrent hemorrhage and they may be maintained in better condition for operation should that prove necessary.

The second factor which probably contributed to our mortality was too strong a conservatism toward invoking surgery. During the period of this study our criteria for surgical interference in the patient with an actively bleeding ulcer have been modified. Originally we felt that only patients 50 years of age or older were candidates for operation. While it is realized that older patients are more likely to require operation, the age factor was discarded as a criterion for surgery since bleeding ulcer may also prove fatal in younger people (Fig. 1).

We do not feel, as do Stewart and associates,[11] that the decision to operate must be made immediately upon admission. Nor are we certain that surgery must be invoked within 48 to 72 hours of the onset of bleeding, although the majority of our patients are operated upon 2 to 3 days after admission. If a patient with bleeding peptic ulcer has two episodes of shock, or one episode of shock with recurrent hemorrhage, or persistent bleeding with failure of red blood cell count and hematocrit to rise after adequate transfusions, then we invoke surgery regardless of the duration of the bleeding.

A review of the literature gives the impression that surgeons, as a rule, believe that bleeding from the upper gastrointestinal tract is a surgical emergency while internists, on the other hand, consider it a medical problem. This difference has probably resulted because the surgeon has too frequently been called in too late to operate upon a patient with bleeding ulcer. To obviate this difficulty we use a team in the management of these patients. The team consists of the medical, surgical, and roentgenological residents consulting with corresponding members of the attending staffs. The patients are subjected to x-ray examination of the upper digestive tract within 24 to 48 hours of admission.

Since gastric ulcers bleed more severely than duodenal ulcers, and are attended with a more serious prognosis, they will more frequently require surgical intervention.

CONCLUSIONS

On the basis of a study of 339 cases of bleeding peptic ulcer admitted to the Cincinnati General Hospital during a ten-year period, the following conclusions are drawn:

1. Bleeding peptic ulcer is much more serious when it occurs after the age of 40 years.

2. Bleeding peptic ulcer appears to be slightly more grave in men and in the white race.

3. The duration of ulcer symptoms prior to hemorrhage is of no prognostic significance.

4. Bleeding gastric ulcers are much more serious than duodenal ulcers, because they bleed more profusely and tend to occur relatively more frequently in older patients.

5. Hematemesis, either preceded or followed by melena, is no more serious than melena alone.

6. Recurrent and continuous hemorrhage are equally grave.

7. The liberal use of blood transfusions and the more frequent recourse to emergency surgery in selected patients should further reduce the mortality from bleeding peptic ulcer.

We wish to acknowledge the assistance of Dr. Ernest Abernathy of the Department of Pathology, Cincinnati General Hospital, who reviewed the pathologic sections for us.

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SURGICAL INTERVENTION IN MASSIVE GASTRODUODENAL BLEEDING

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IN A previous communication,[1] after reviewing some of the more significant contributions to the literature of massive gastroduodenal hemorrhage, I presented a preliminary report on the experiences at the Roosevelt Hospital with a fairly large group of severe bleeders. The plan of treatment incorporated in that report has developed into a well-defined policy, flexible enough, however, to permit the individualization which we feel is so necessary and so desirable. I wish now to report on our further experience with gastroduodenal hemorrhages and to discuss briefly certain additional considerations which may be of value in the management of these difficult and trying problems.

It is of fundamental importance in the consideration of massive gastroduodenal bleeding that we restrict the discussion to that group of patients in whom hemorrhage has been acute, rapid, profuse, and an immediate threat to life. In my previous report and in the present one, I have eliminated from consideration all patients in whom the hemorrhage did not produce clinical shock as ordinarily defined, irrespective of the low levels to which hematocrit and erythrocyte determinations may have fallen. The slow bleeder who gradually develops a profound anemia during the week prior to admission to the hospital does not, in my opinion, belong in the acute massive hemorrhage group. To be sure, his problem is an important one; he requires blood and should be given plenty of it, but ordinarily there is no need to take out his stomach in the middle of the night.

It has become quite apparent to all of us that in recent years, as a consequence of improved medical management, chiefly the use of massive transfusions, the reduction in mortality among patients with massive gastroduodenal bleeding under conservative treatment has been most impressive. However, deaths still occur from ulcer hemorrhage, and post-mortem examination in the fatal cases frequently reveals lesions which might have been resected without undue difficulty or risk. The problem then, stated in the simplest terms, is to select judiciously from the very large number of ulcer bleeders a relatively small group in which we have learned from past experience that the risk of conservative treatment is intolerably high.

What type of patient do we find in this small group who are in such grave danger, and in whom emergency operation should seriously be considered? In my experience he (or she) presents the following qualifications, in general:

1. He is usually over 45 years of age.
2. He has lost blood rapidly enough, and in such quantity, as to have produced hemorrhagic shock.

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3. The hemorrhage has been manifested by vomiting of red blood, rather than by coffee-ground vomitus or melena alone.
4. Bleeding, after the initial hematemesis, is then repeated or persistent, and may be manifested by either vomiting or melena.

These qualifications require comment and I should like to discuss them in the order in which they have been presented.

1. Age of the Patient.—The effects of sudden hypotension and critical acute anemia in the older patient are well known. Prolonged hypotension and persistent anemic anoxia will induce tissue changes which often cannot be undone by subsequent restoration of blood values. On the other hand, the younger patient is much more resistant to the disastrous effects of severe exsanguination. However, he is by no means immune to the lethal danger which threatens the older patient. Though younger patients will require emergency operation much less frequently than the older group, the youth of the bleeder should not lull us into complacency.

2. Shock.—Slow bleeding is usually manifested by melena alone, or by emesis of "coffee-ground" material, but it may eventually produce extraordinarily low blood levels. However, in the absence of shock there is no immediate threat to life. While emergency operation is seldom necessary in the slow bleeder, adequate blood replacement is of major importance if serious anoxic changes in vital organs are to be avoided.

3. Vomiting of Blood.—Vomiting of a large quantity of red blood is a serious prognostic sign since it usually indicates rapid bleeding, with rapid distention of the stomach or duodenum. In our experience an ulcer hemorrhage which has manifested itself only as melena is rarely fatal. In the series I am now reporting there were two deaths as a result of hemorrhage which was exhibited only as "liquid bloody" or "tarry" stools without hematemesis. (Both of these patients received blood in quantities which we would not consider adequate today.) However, it is important to remember that pyloric obstruction of sufficient degree to impede regurgitation from the duodenum into the stomach may mask rapid hemorrhage from a postpyloric lesion. In Pedersen's[7] series, among the fatal cases, there was hematemesis in 85 per cent and melena alone in 15 per cent.

4. Repeated Bleeding.—A patient who has suffered an initial profuse hematemesis has established the fact that he is bleeding from a vessel of considerable size. Thereafter, continued bleeding, whether by mouth or bowel, is of serious prognostic importance.

EPIGASTRIC PAIN AND MASSIVE HEMORRHAGE

Persistent "ulcer pain" in the severe bleeder has always been regarded as a most ominous sign.[2, 3] The epigastric distress has usually been attributed to deep penetration of the ulcer or to impending perforation. This, undoubt-

edly, is true in many cases. In a considerable number of patients complaining of such pain we have found, however, that electrocardiograms have demonstrated an acute coronary insufficiency, often with definite myocardial infarction. To date we have made this observation chiefly, as might be expected, in the older group of patients. The damage is undoubtedly a consequence of hypotension and anoxia. The pain is quite easily confused with so-called ulcer pain, especially in a patient who is already in mild or severe shock from hemorrhage. The differentiation is obviously of crucial importance. Myocardial ischemia with anginal pain, the pain erroneously interpreted in the past as due to a deeply penetrating bleeding lesion, may account for the reputedly high mortality among the bleeders who had persistent epigastric distress.

THE INDICATIONS FOR EMERGENCY OPERATION

It is wrong, I think, to operate upon any patient who is having severe gastroduodenal bleeding unless the diagnosis of peptic ulcer, or some other lesion amenable to emergency surgery, has been established with reasonable certainty. Roentgenologic confirmation should be attempted, if necessary, and when possible. Esophageal studies will frequently demonstrate varices in patients with portal hypertension. Blood dyscrasias may be detected in routine emergency studies. The most rewarding diagnostic procedure, however, is still a good clinical history and a careful physical examination.

The most urgent indication for emergency operation, in my opinion, is *continued severe bleeding.* The fact that a patient responds to blood transfusion by recovery from shock levels is of little comfort if his ulcer persists in bleeding profusely. Our present methods of rapid replacement of lost blood certainly permit us to maintain a reasonable pressure in the face of all but the most furious types of hemorrhage. But there is small profit in forcing enormous quantities of precious blood indefinitely into a system which pours it out almost as fast as it receives it. Under these circumstances one may justifiably conclude that surgical intervention is not a radical procedure, particularly since it may be carried out, in our experience, with an acceptable operative risk.

More specifically, the indications for emergency surgery in these individuals may be summarized as follows:

1. Patients in the *older* age group who have had profuse hematemesis, and who show signs of continued bleeding over a period of twelve to twenty-four hours, require surgical intervention. The larger the quantity of blood needed to maintain systolic pressure above shock levels, the sooner the operation is performed.
2. Patients in the younger age group who continue to bleed severely may be observed for slightly longer periods, providing that satisfactory pressure is maintained with reasonable quantities of transfused blood. In any case, however, a delay in operation beyond the forty-eight-hour period increases the operative risk.

3. Recurrent hemorrhage in any patient, but particularly in the older ones, whether it occurs days or weeks after the initial episode, is an absolute indication for immediate operation.
4. Since a severe hemorrhage superimposed upon a known pyloric obstruction is difficult to appraise clinically, it is best treated by early operation.
5. Simultaneous hemorrhage and perforation obviously demand immediate operation. Since many of these patients are bleeding from an ulcer *other than the one which has perforated,* the surgeon must be prepared for more than the usual simple closure of the perforation.

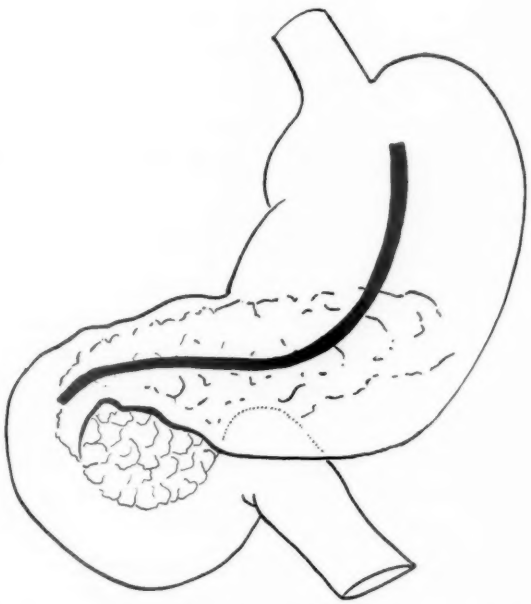

Fig. 1.—A wide gastrotomy is employed in the occasional case in which simple inspection and palpation fail to reveal the bleeding lesion. Pyloroduodenotomy is add, if necessary.

IDENTIFICATION OF THE LESION AT OPERATION

At operation the vast majority of bleeding lesions of the stomach or duodenum are readily located. However, if inspection and careful palpation fail to reveal the ulcerated area, a wide gastrotomy, and pyloroduodenotomy if necessary (Fig. 1), is performed before gastrectomy is undertaken. I am not convinced of the wisdom of proceeding with subtotal resection of the stomach[5] if the source of hemorrhage is not positively identified. Small ulcerations, not disclosed by palpation, have been found by careful inspection through a wide gastrotomy. On a number of occasions these small ulcerated areas were located well above the line of transection ordinarily selected in partial gastrectomy, and these lesions might very possibly have been left behind if a so-called "blind gastrectomy" had been performed. On one occasion, one of my colleagues had already transected the stomach, when in performing the

anastomosis, he fortunately and quite by accident discovered the bleeding lesion in the residual gastric pouch. A quick transection at a higher level avoided possible further embarrassment. In one of my own patients, after a painstaking examination of the interior of the stomach and immediate postpyloric area, the bleeding point was ultimately found in the third portion of the duodenum. A small coneshaped aneurysm of the anterior wall of the aorta, the result of a previous injury, had ruptured into the lumen of the duodenum.

The gastrotomy which I am advocating will be necessary only on rare occasions since most surgical lesions are quickly discovered on palpation. It is futile, however, to attempt to inspect the gastric and duodenal mucosa through a three or four inch gastrotomy. If gastrotomy is employed at all it must be wide enough to permit actual visualization of the entire stomach cavity, the incision being carried, if necessary, through the pylorus and first portion of the duodenum. If the field is carefully walled off with abdominal pads there should be no significant contamination of the operative area. When done gently and expeditiously, exploratory gastrotomy should not add to the trauma of the operation.

THE OPERATIVE PROCEDURE

With the exception of one patient in whom simple duodenotomy and ligation was performed unsuccessfully at late operation and another in whom simple gastrotomy revealed hemorrhage from esophageal varices, a standard subtotal gastrectomy was performed in all patients who came to surgery. With adequate preparation and continued support during the operative procedure, these individuals tolerate major surgery extraordinarily well. There is no reason for undue haste in accomplishing the operation nor is there, in my opinion, any need or justification for the employment of palliative procedures such as gastroenterostomy alone, or simple ligation of bleeding vessels.

A gastric ulcer ordinarily presents no special technical problems. A duodenal ulcer, on the contrary, eroding into adjacent tissues, may confront the surgeon with almost insurmountable difficulties. Since some of these lesions will be found to have penetrated almost a centimeter deep into the head of the pancreas, it is folly to insist that "the ulcer must always be removed." The ulcer should be removed *if it is safe and feasible to do so.* I think it is imperative that the pylorus and a cuff of duodenum be included in the specimen. This insures complete excision of the antral and pyloric mucosa. In cases in which the ulcer has burrowed so deeply into the pancreas that the crater cannot be removed, the resection may be done around the ulcer, in accordance with numerous accepted and well-known techniques. The method suggested by Graham[4] and depicted with modifications in the accompanying sketches (Fig. 2) shows the ulcer excluded from the duodenum. For the very large, deeply penetrating ulcer the technique proposed by Nissen[6] is very effective and easily performed. Other procedures, such as that described by Wangensteen,[8] leave a nonresectable ulcer within the duodenal stump. Irrespective of the method of resection one employs, however, if the ulcerated area is left

behind, it is most essential that the bleeding point be securely transfixed with fine silk sutures. This will insure against fresh bleeding. A pledget of hemostatic gauze may be used to cover the transfixed area.

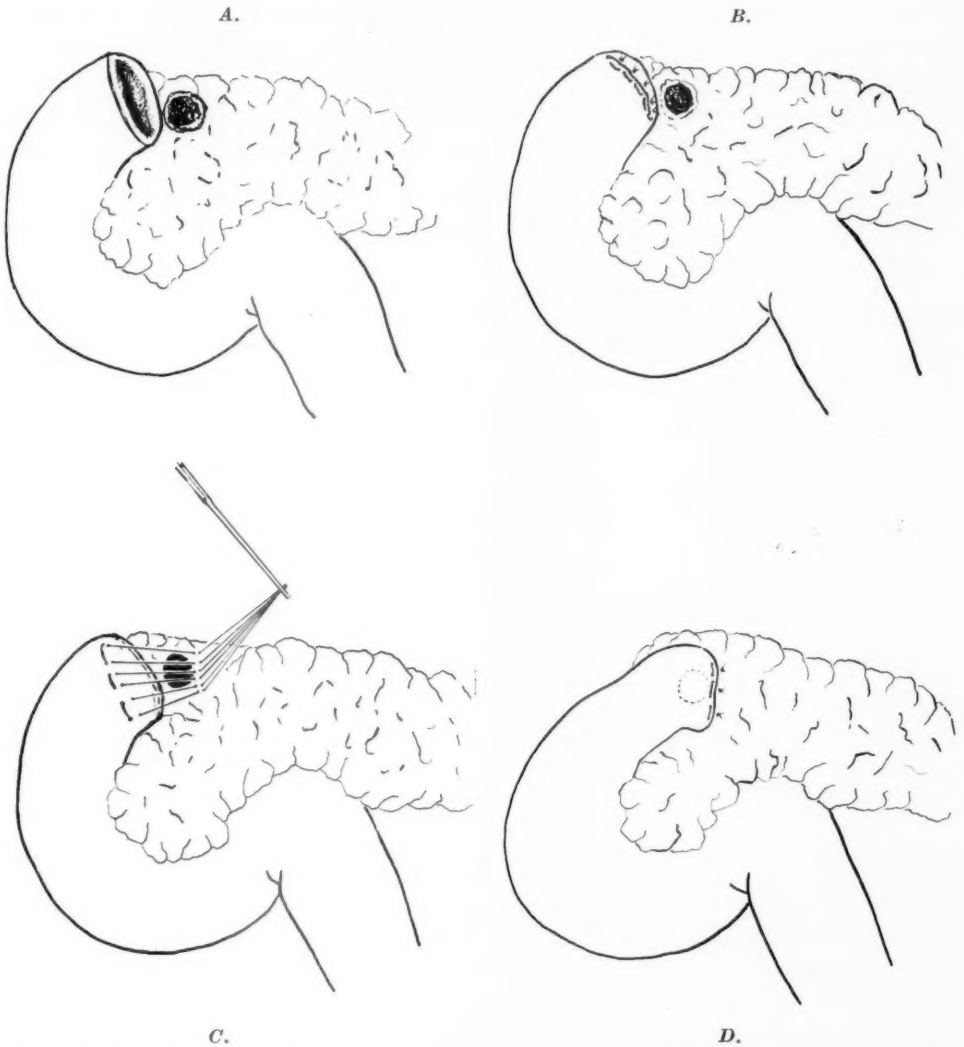

Fig. 2 (Modified from Graham).—*A*, The duodenum has been transected distal to the ulcer. Stomach segment, pylorus, and a cuff of duodenum have been removed.

B, The duodenum distal to the ulcer is closed with interrupted sutures of fine silk.

C, Three interrupted silk sutures are introduced so that when tied they will roll the closed duodenal stump over the ulcer crater.

D, The ulcer crater is completely covered by the duodenal stump.

RESULTS

Our experience during the past seven years is summarized in the accompanying tables (Tables I, II, III). Only those patients have been included who suffered a massive hemorrhage as defined above. During the earlier years covered in this report, we had no well-defined policy with respect to the management of gastroduodenal bleeding. Early emergency operation was rarely

performed and, in general, blood replacement was inadequate in quantity if judged by the standards now in use. Mortality following conservative management or late operation, particularly in older patients, was prohibitive.

TABLE I. OPERATION WITHIN FORTY-EIGHT HOURS OF ONSET OF MASSIVE BLEEDING*

PATHOLOGY	NUMBER	DEATHS
Gastric Ulcer (single and multiple)	10	0
Duodenal Ulcer	22	1
Gastric and Duodenal Ulcers	4	0
Gastrojejunal Ulcer (anastomotic)	2	0
Esophageal Varices	1	1
Total	39	2 (5.1%)

*All patients were operated upon during the active bleeding phase.

TABLE II. CONSERVATIVE MANAGEMENT*

AGE	NUMBER	DEATHS	MORTALITY (PER CENT)
Over 50 years	77	13	16.9
Under 50 years	42	2	4.8
Total	119	15	12.6

*The quantity of blood administered to some of these patients, chiefly in the 1943-1947 group, would not be considered adequate today. Many, however, received more than 5,000 c.c. There were only two fatal cases in which bleeding had been manifested as melena alone.

TABLE III. LATE OPERATION*

AGE	NUMBER	DEATHS	MORTALITY (PER CENT)
Over 50 years	9	4	44
Under 50 years	6	2	33
Total	15	6	40

*These patients were subjected to operation because of persistent hemorrhage, and while bleeding actively, but operation was performed more than two days after the onset of hemorrhage. This group falls chiefly into the 1943-1947 series. One patient in this group received 12,500 c.c. of blood during nine days of bleeding before operation. She died of uremia on the fifth postoperative day.

Since the adoption of the policy described above, our results have been most encouraging. There have been only two deaths among the thirty-nine patients upon whom early operation was performed. One of these fatalities was an elderly physician afflicted with an advanced cirrhosis of the liver, and bleeding furiously from cardioesophageal varices. He died of liver insufficiency six days after simple gastrotomy. The other death occurred in a patient who was known to have hemophilia and a peptic ulcer. Operation upon this man was undertaken as a desperate lifesaving measure, and with complete awareness of the great risk involved. He continued to bleed slowly from all suture lines and, despite the administration of enormous quantities of blood, succumbed to his disease on the eighteenth day after operation.

At the present time, any patient admitted to the Roosevelt Hospital suffering from severe gastroduodenal bleeding is seen upon admission by both the Surgical and the Medical Services in consultation. The patient is then assigned routinely to the Surgical Service. If emergency operation is not required, the patient is transferred to the Medical Service on the third or fourth day. The surgeons, thereafter, are notified at once if bleeding recurs.

SUMMARY

1. Among the large number of patients suffering severe gastroduodenal hemorrhages there is a relatively small group upon whom emergency operations should be performed. This group will consist chiefly, though not exclusively, of older patients who have vomited bright red blood and who have shown signs of hemorrhagic shock. The decision for emergency operation in such a patient should be based, not on his response to adequate blood replacement, but rather on clinical signs of continued severe bleeding.

2. Recurrent hemorrhage at any time after the initial episode, particularly in the older patient, demands surgical intervention.

3. The patient in whom blood loss is manifested only as melena is in less danger of exsanguination than the patient who vomits bright blood. However, pyloric stenosis will occasionally mask rapid bleeding from a duodenal lesion by impeding regurgitation into the stomach.

4. Persistent epigastric pain in the presence of severe ulcer bleeding is frequently due to myocardial ischemia or actual myocardial infarction rather than to deep penetration of the ulcer.

5. A patient with severe gastroduodenal bleeding should not be subjected to operation unless the diagnosis of peptic ulcer, or some other lesion amenable to surgery, has been established with reasonable certainty.

6. Early operation may be undertaken with much less risk than operation performed after many days of persistent or recurrent hemorrhage.

7. At operation it is wise to identify the source of the hemorrhage before proceeding with gastrectomy. Wide gastrotomy, and pyloroduodenotomy if necessary, should be employed in the occasional case in which palpation of the stomach and duodenum fails to disclose the bleeding lesion.

8. Subtotal gastrectomy is the most effective operative procedure for bleeding peptic ulcer. There is no justification for the employment of gastroenterostomy alone, or for simple ligation of blood vessels supplying the duodenum and stomach.

9. At the Roosevelt Hospital, among thirty-eight patients subjected to emergency subtotal gastrectomy for massive gastroduodenal bleeding, there was only one fatality, this occurring in an ulcer patient known to be suffering from hemophilia. Following gastrotomy alone there was a late fatality due to hepatic insufficiency in an elderly patient who at operation was found to be bleeding from cardioesophageal varices.

10. When operation is indicated for massive gastroduodenal bleeding, emergency subtotal gastrectomy, if performed early, may be done without significantly greater risk than the elective operation.

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THE ROLE OF TRYPSIN IN THE PATHOGENESIS OF ACUTE HEMORRHAGIC PANCREATITIS AND THE EFFECT OF AN ANTITRYPTIC AGENT IN TREATMENT

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SINCE the first reported description of acute hemorrhagic pancreatitis by Fitz in 1899,[16] a large literature has developed concerning the experimental and clinical aspects of the disease.[33, 42] There have been direct investigations of the pathogenesis of this syndrome and several possible etiological mechanisms have been suggested on the basis of experimental animal studies.[30, 35, 36] None of these have been fully accepted. Bockus states, "It is generally accepted that the pathological changes of acute pancreatic necrosis are due to the effect of activated pancreatic ferments on the tissues," but offers no direct evidence to support this.[1] In a recent review, Howard[23] suggested that an elevation of serum trypsin concomitant with the elevation of serum amylase and lipase would be expected, but that accurate methods for the detection of this enzyme in serum are lacking. Using a qualitative test he demonstrated that active trypsin is present in the peritoneal fluid of patients with acute pancreatitis.

The serum of human beings, dogs, and other species is known to contain an antiproteolytic agent which is active in suppressing the proteolytic effect of trypsin.[5, 10, 19, 25] This antiproteolytic factor is elevated in a number of clinical conditions.[7, 9, 13, 22] In the course of investigating the titer of antiproteolytic activity in patients with malignant disease we noted that a few patients of the control series recently recovered from acute pancreatitis showed a considerable elevation in antiproteolytic activity. It is known that the injection of trypsin into experimental animals will lead to a rise in the titer of antiproteolytic activity[6, 19, 25] and it was suggested that the elevation of antiproteolytic activity in these patients might have been due to absorption of trypsin freed from the pancreas.

Recently an accurate quantitative test for the determination of proteolytic activity in serum was developed in this laboratory.[14] With this test, a study of the changes in the proteolytic and antiproteolytic activity of serum in experimental acute pancreatitis was undertaken.

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The investigation of Kunitz, in 1945, resulted in the isolation from soy bean meal of a crystalline protein active in the inhibition of the proteolytic action of trypsin.[26-28] Previous study in this laboratory has shown this inhibitor to be nontoxic in mice and effective in decreasing proteolytic activity and elevating antiproteolytic activity in the serum of mice in vivo.[37]

Because of the evident increase of proteolytic activity of the serum with experimental pancreatitis, we next investigated the use of an antiproteolytic material (soy bean inhibitor) to control this increased proteolytic activity.

MATERIALS

1. Twelve mongrel dogs fed on Purina Dog Chow and given water ad libitum were used in these experiments. Nine of the dogs weighed from 19 to 23 kilograms and were used as controls and in the induction of experimental pancreatitis. Three dogs weighed 7 to 9 kilograms. These smaller dogs were used in the experiments where trypsin inhibitor was employed in order to conserve the supply of inhibitor.

2. Soy bean trypsin inhibitor (hereafter also termed SBI) was prepared according to the method of Kunitz[26] but not reduced to the completely pure state. This material assayed at 60 per cent of purity.*

3. Staphylokinase was prepared by the method of Ferguson.[15]

METHODS

Acute hemorrhagic pancreatitis was induced in dogs by the method described by Rich and Duff.[36] The dogs were anesthetized with Nembutal using 0.7 c.c. of a 2 per cent solution per kilogram. Using sterile technique, the abdomen was entered through a vertical midline incision. The duodenum was exposed and opened in a longitudinal direction. The papilla marking the mouth of the duct of Santorini was located and cannulated with a blunt No. 19 needle. Bile was aspirated into a syringe from the dog's gall bladder, and injected forcibly into the duct at a pressure exceeding 18 cm. of water. The 9 dogs weighing over 19 kilograms were injected with 10 c.c. of bile. Dogs weighing less than 10 kilograms were injected with 5 c.c. of bile. The effect of the injection could be observed readily since the entire pancreas turned green brown in color and petechial hemorrhages developed within a few minutes. The duodenum was then closed with a single layer of inverting silk sutures and the abdomen was closed in layers with interrupted silk sutures. Dogs used as controls were submitted to exactly the same procedure except that following cannulation of the accessory duct the needle was removed and bile was not injected.

Blood pressure was recorded through a cannula placed in the left femoral artery. The cannula was connected by a tube with a mercury manometer. The system was filled with a 2 per cent heparin solution in saline. The heparin solution was not allowed to enter the arterial system. A continuous recording of the pressure was made on a kymograph.

*Supplied by Parke, Davis & Co. Laboratories, Detroit, Mich., through the kindness of Dr. E. Loomis.

Three dogs were injected intravenously with a 2 per cent solution of SBI in saline five minutes after pancreatitis was induced.

Antiproteolytic and proteolytic activity of the serum was determined by methods previously described.[5, 14] The proteolytic activity was recorded in terms of milligrams of tyrosine released from a substrate of casein following incubation for 24 hours with a precipitate of the euglobulin fraction (plasminogen) of serum.[14] The antiproteolytic activity was expressed in terms of the greatest dilution of serum which would inhibit a standard quantity of trypsin.[5]

Amylase was determined by the Clark[4] modification (colorimetric) of the Somogyi method.[38] Clotting times were done on those dogs receiving SBI by the method of Lee and White.[44]

Autopsies were performed on all animals. The control dogs and the dog which survived pancreatitis were sacrificed and autopsied on the seventh day. The animals which died in the course of experiments were autopsied as soon after death as possible.

RESULTS

Pancreatitis was induced in 9 dogs. Six of these dogs received no treatment. Five of these 6, designated D, E, F, G and I, died—3 within 12 hours and 2 within 24 hours. The remaining dog (H) survived to be sacrificed on the seventh day. The 3 control dogs, designated A, B, and C, all lived until the seventh day when they were sacrificed. As shown in the scattergram (Fig. 1) the serum amylase rapidly rose to high levels in all experimental animals with pancreatitis as compared with the controls.

BLOOD PRESSURE CHANGES

Systolic blood pressure fell rapidly following the production of pancreatitis in the dogs. In the dogs which died, the pressure fell to shock levels and remained in the shock range as long as the pressure was recorded or until the dogs died (Fig. 2). In the surviving dog there was also a profound drop in blood pressure but the pressure returned to normal levels in one hour and to the original level of 140 mm. in 4 hours (Fig. 3).

CHANGES IN SERUM ENZYME ACTIVITY

In the dogs which had a severe reaction to the induced pancreatitis and subsequently died, the spontaneously activated serum proteolytic activity increased markedly following the production of pancreatitis and then fell to normal or below from 2 to 12 hours after the onset of pancreatitis (Fig. 4, *B*). Dog H, the only survivor, differed in having a lower initial proteolytic activity and in showing a minimal increase in this activity after the induction of pancreatitis (Fig. 4, *B*). The control dogs showed practically no variation in the proteolytic activity during the 24 hours in which they were tested (Fig. 4, *A*).

The antiproteolytic titer showed a progressive fall after the induction of pancreatitis (Table I). In the 4 dogs that succumbed (D, E, F, and G), the antiproteolytic titer reached very low levels before death. The surviving dog (H) showed a minimal decrease in the antiproteolytic activity and in 48 hours

the titer had risen to above normal. This high antiproteolytic level was maintained. The control dogs showed only slight fluctuation of the proteolytic and antiproteolytic activity (Table I).

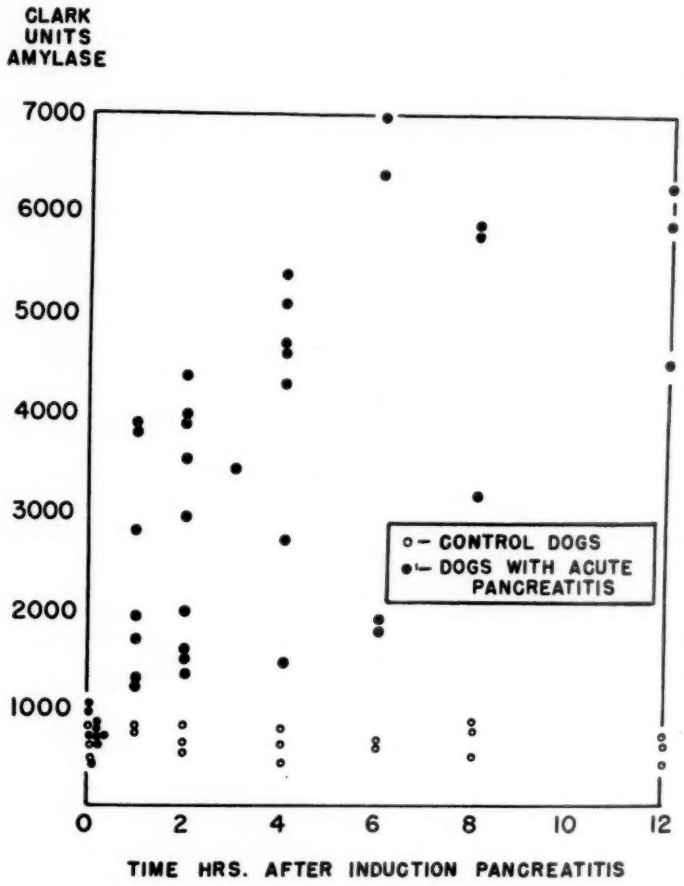

Fig. 1.

EFFECT OF SBI INJECTIONS

Injections of SBI intravenously in the dogs produced a profound change in the proteolytic and antiproteolytic activity of the serum in the course of induced pancreatitis. Dog J, the first dog injected with SBI, received 500 mg. per kilogram. This dose, calculated on the basis of results in mice, was much too high. The blood in this dog failed to coagulate (Table II) and oozing of blood occurred from every point in the operative site. This animal died from hemorrhage in four hours. Blood drawn during the four-hour period before death showed that the proteolytic activity of the serum dropped to zero (Fig. 4, *C*) and the antiproteolytic activity was markedly elevated (Table I). A lesser decrease in coagulability of blood also had been observed in mice receiving large doses of SBI.[37]

The two dogs (K and L) subsequently treated with SBI were given 100 mg. per kilogram. In both these dogs the proteolytic activity was maintained at

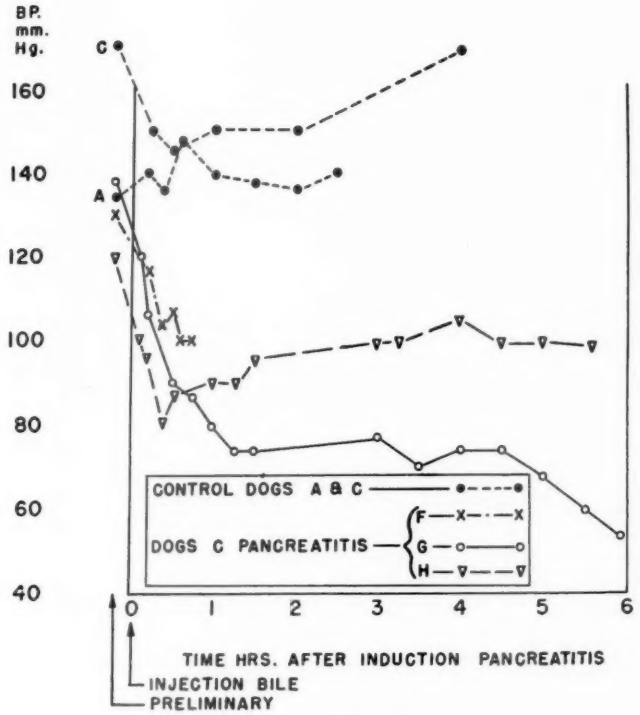
BP. mm. Hg.
160
140
120
100
80
60
40
C
A
CONTROL DOGS A & C
DOGS C PANCREATITIS
F
G
H
0 1 2 3 4 5 6
TIME HRS. AFTER INDUCTION PANCREATITIS
INJECTION BILE
PRELIMINARY

Fig. 2.

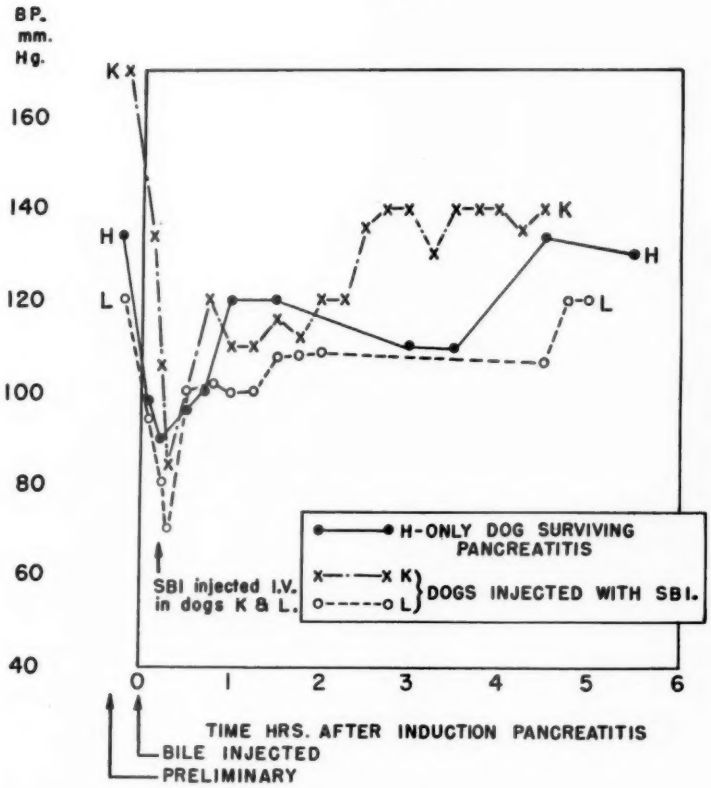
BP. mm. Hg.
160
140
120
100
80
60
40
K
H
L
H-ONLY DOG SURVIVING PANCREATITIS
K
L
DOGS INJECTED WITH SBI.
SBI injected I.V. in dogs K & L.
0 1 2 3 4 5 6
TIME HRS. AFTER INDUCTION PANCREATITIS
BILE INJECTED
PRELIMINARY

Fig. 3.

levels within the normal range (Fig. 4, *C*). The antiproteolytic levels rose significantly following injection of the SBI and then began to drop, but did not fall below the original level in either of the two dogs (Table I). The blood pressure in SBI treated dogs, K and L, showed the same profound drop on the

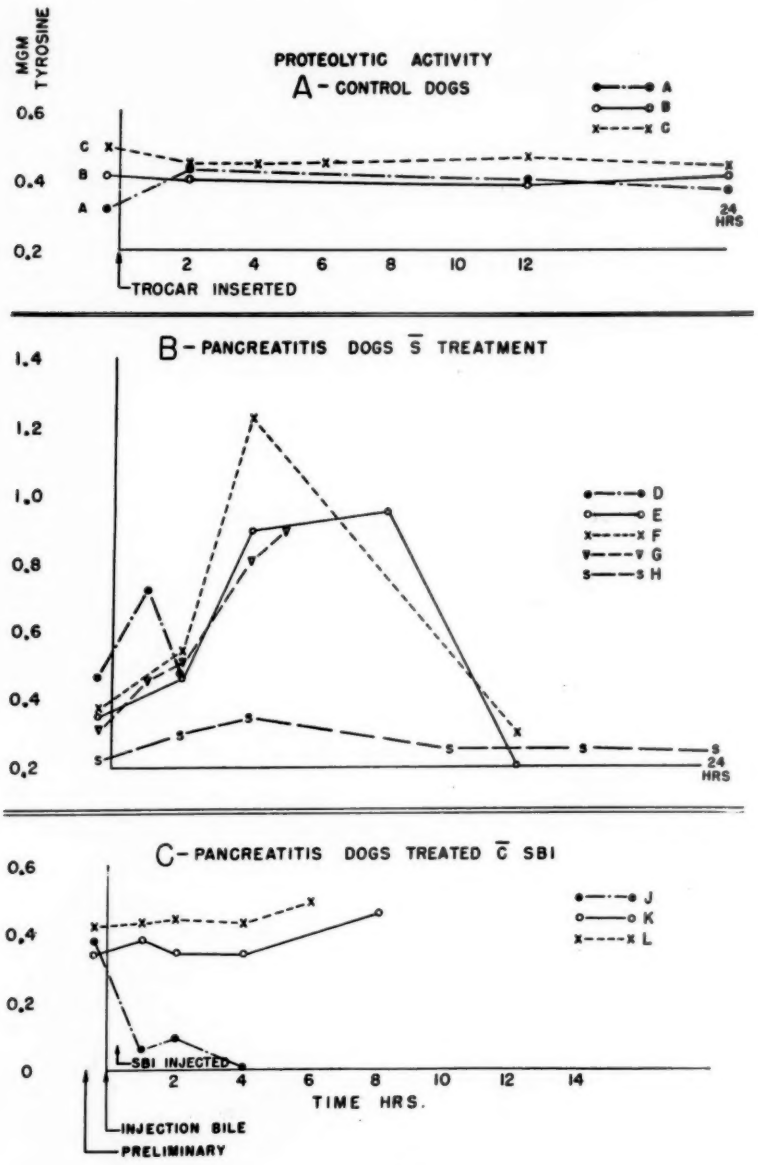

Fig. 4.

induction of pancreatitis, but on injection of SBI the blood pressure rose rapidly, returning to normal levels in one-half hour and one and one-half hours respectively (Fig. 3). Both dogs became quite light under anesthesia in 4 hours compared to the untreated dogs with pancreatitis which remained in shock and in coma until death.

TABLE I. ANTIPROTEOLYTIC ACTIVITY IN DOGS WITH EXPERIMENTAL ACUTE PANCREATITIS, INCLUDING THE EFFECT OF INJECTING SOY BEAN TRYPSIN INHIBITOR

DOG	TREATMENT	PREOPERATIVE	POSTOPERATIVE TIME (IN HOURS)									
			1	2	4	6	8	12	24	48	72	120
A	Control	40		60	50		60	40	50	60	70	80
B	Control	70	70	50	50	70		90	90	90	90	60
C	Control	60		60	60	40		60				60
D	Pancreatitis	60	50	30				Died < 12 hr.				
E	Pancreatitis	80	40	30	50			20	Died << 24 hr.			
F	Pancreatitis	60		40	30		30	20	Died << 24 hr.			
G	Pancreatitis	80	50	60	50	10		Died < 12 hr.				
H	Pancreatitis	80		70	80	50	60	60	70	120+		120+
J	Pancreatitis & 3 Gm. SBI	60	120+	100	70	Died in 4 hr.						
K	Pancreatitis & 1 Gm. SBI	40	100	70	60		50		Died in 24 hr.			
L	Pancreatitis & 1 Gm. SBI	60	90	60	50	60	Died due to tech. error 6 hr.					

Unfortunately dog L became so light that he tore loose the cannula in the femoral artery in the course of his struggles. This dog exsanguinated on the table. Dog K recovered rapidly from the anesthesia and was returned to his cage. He remained active and vigorous during the day, taking water and walking about without difficulty. Twelve hours following operation he appeared weaker and in 24 hours he had died. Clotting time was markedly prolonged following injection of SBI in both dogs but returned to normal in 8 hours in dog K and in 6 hours in dog L (Table II).

TABLE II. CLOTTING TIME (IN MINUTES) IN DOGS WITH PANCREATITIS WHO RECEIVED SBI INTRAVENOUSLY

DOG	TREATMENT	BEFORE R	TIME AFTER R (IN HOURS)				
			1	2	4	6	8
J	500 mg./kg.	5	480+	480+	480+	480+	
K	100 mg./kg.	6	33.5	20	15		5
L	100 mg./kg.	8	28	20	12	4	

ACTIVATION OF PLASMINOGEN BY STAPHYLOKINASE

The plasminogen (proteolytic enzyme precursor)[3] from the serum of several dogs in whom pancreatitis had been produced was activated by staphylokinase.[17] In many cases the resulting proteolytic activity was so high that it was impossible to determine it accurately with the methods used. In those cases where it could be determined several changes were noted. In dog J which received 500 mg. SBI per kilogram the total proteolytic activity in the control serum after activation with staphylokinase was 1.150 mg. of tyrosine. After induction of pancreatitis and injection of SBI, no proteolytic activity could be found in the activated serum within four hours. Thus the serum contained no spontaneous activity and no activity could be induced with staphylokinase. In dog L, which received 100 mg. of SBI per kilogram, the spontaneous proteolytic activity remained normal despite the production of pancreatitis, and the serum responded in the usual fashion to activation by staphylokinase with a rise in the level of activity from 0.395 to 1.150.

POST-MORTEM FINDINGS

All dogs dying with pancreatitis, including those injected with SBI, showed a diffuse hemorrhagic necrosis of the pancreas with extensive fat necrosis. The degree of necrosis varied somewhat with the length of time the animal survived before death occurred. Dog H, which survived the induced pancreatitis, was autopsied on the seventh day and the pancreas was found grossly to be quite firm and indurated throughout. No fat necrosis was found at this time. The controls, autopsied on the seventh day showed nothing more than adhesions about the operative site.

DISCUSSION

From the preceding data it is apparent that a rise in the spontaneous proteolytic activity of the serum occurs in the course of acute hemorrhagic pan-

creatitis. This may come from one or both of two sources. It may be due to the release of active trypsin from the injured pancreas or it may be due to the transformation of plasminogen (proteolytic enzyme precursor) of the serum into the active form, plasmin.[3] In the method used for determining proteolytic activity the euglobulin fraction of serum is precipitated and analyzed. This fraction contains plasminogen.[5, 19] The fraction is not washed in this method[14] and may carry small amounts of other fractions with it. Whether trypsin actually comes down in the precipitate is not known but it is possible that if free trypsin were present in the serum at least a portion of it would be precipitated.

In the dogs in which pancreatitis had been induced there was a suggestion on the basis of the results in plasminogen activated with staphylokinase that at least some of the increase in proteolytic activity noted was due to an activation of the serum proteolytic enzyme in vivo. However, the evidence was too scanty to present at this time.

The rapid drop in antiproteolytic activity noted in dogs with pancreatitis is further evidence of the increase in proteolytic activity in the serum. As the proteolytic activity increases, the antiproteolytic factor of serum would be expected to combine with it to preserve the normal level. The level of antiproteolytic activity at any moment probably represents material remaining after equilibrium has been reached with (1) the trypsin being released from the injured pancreas, and/or (2) the plasmin produced by activation of plasminogen in the serum. It is noted that death in the dogs occurred following the fall of antiproteolytic activity to very low levels. Presumably the defenses of the serum against toxic effects of proteolysis were exhausted. The only dog which survived was that in which the proteolytic activity failed to increase markedly.

Although it has usually been assumed that some trypsin was released in the circulation in the course of pancreatitis, an increase in the proteolytic activity in the serum has never been directly demonstrated in the past. While many have felt that some of the toxic symptoms noted in pancreatitis were due to free trypsin in the blood stream others have argued that trypsin could not be expected to cause toxicity since it has been shown repeatedly not to affect living cells.[34] On the other hand the injection of trypsin intravenously has been demonstrated to cause profound shock and death in dogs and other experimental animals.[32, 39] The shock is due both to intravascular clotting caused by trypsin and to the proteolytic activity of the enzyme.[39]

Shock is a prominent feature in the initial stages of the more severe cases of acute hemorrhagic pancreatitis.[33, 42, 43] Bockus states, "Collapse may occur rather quickly. Usually the pulse rate is rapidly accelerated, pulse volume diminishes, the blood pressure falls, and the skin becomes cold and clammy and a peculiar cyanosis may develop. The cause of death is usually attributed to a toxemia of undetermined type, although it seems more closely related to the profound shock which is so striking in those cases which terminate fatally. In the older statistics, in which fewer of the relatively mild cases were included, the mortality was in the neighborhood of 50 per cent."[1] There is considerable

evidence that both a rise in proteolytic activity and a fall in antiproteolytic activity as observed in these experiments could contribute to fatal shock. Numerous experiments have demonstrated the shocking effect of injections of trypsin and other proteolytic enzymes in experimental animals.[32, 39, 41] Converting plasminogen to the active plasmin in vivo by the intravenous injection of staphylokinase causes profound shock and death in the dog.[6, 29] Removing the antiproteolytic factor from the circulation in dogs by adsorbing it on intravenously injected kaolin resulted in shock and death.[24] It has been shown that plasminogen spontaneously is transformed to active plasmin in the absence of the inhibiting action of the antiproteolytic agent of serum.[2] Thus the introduction of trypsin to the circulation from the pancreas and the reduction of antiproteolytic factors in serum resulting from the addition of trypsin could both be contributing factors to shock in acute pancreatitis.

The intravenous clotting caused by trypsin in experimental animals is especially interesting in relation to pancreatitis in humans. While a change in the clotting time has not been demonstrated in patients with pancreatitis, thrombophlebitis is a frequent complication in this disease, and thrombosis of large vessels is often noted in carcinoma of the body of the pancreas.[18]

The effect of soy bean trypsin inhibitor on the course of pancreatitis is further evidence of the role of proteolytic activity during the profound shock noted in the initial stages. Unfortunately, our supply of SBI was quite limited and only a few dogs could be treated with the material at hand. However, both dogs in which the antiproteolytic titer was elevated artificially with proper amounts of SBI showed a rapid rise of blood pressure to normal levels. Of the six dogs given pancreatitis and not injected with SBI only one dog showed a comparable rise (Fig. 3) and this was the dog which survived. In the one dog which could be followed adequately after induction of pancreatitis and injection of SBI there was a biphasic response with a marked clinical improvement followed by a return to shock and then death. Examination of Fig. 4, *C* shows that both dogs which received 100 mg. per kilogram of SBI maintained a proteolytic titer in the normal range for the first 4 or 5 hours but then showed a tendency for the proteolytic titer to rise again. Furthermore, the clotting time had returned to normal, evidence that the injected SBI was depleted. It is possible that if dog K had received another gram of SBI at 6 or 8 hours and at intervals thereafter he might have survived.

That SBI prolongs the clotting time of blood has been frequently demonstrated in vitro.[12, 20, 31, 40] That it is powerfully effective in vivo is evident in these experiments (Table II). It may well have considerable potentiality for clinical use as an anticoagulant as well as a specific agent in the treatment of the shock stage of acute pancreatitis.

Subsequent to our beginning this project Coffey, Brinig, and Gillespie[11] presented a paper in which they noted a fall in antiproteolytic titer of serum in the acute phase of clinical and experimental pancreatitis. They interpreted this as indirect evidence of a rise in serum trypsin during pancreatitis. They also are working with SBI and feel that it exerts a beneficial effect on the course of acute pancreatitis.

SUMMARY AND CONCLUSIONS

1. Changes in the amylase, proteolytic, and antiproteolytic titers and in blood pressure were observed in a series of dogs with experimental acute pancreatitis.

2. Five dogs died following the induction of pancreatitis. They showed deep shock with an elevation of proteolytic titer and a sharp fall in serum antiproteolytic activity.

3. One dog lived following the induction of pancreatitis. He showed a drop of blood pressure to shock level and then a return to normal. There was only a mild rise in proteolytic activity and little drop in antiproteolytic activity.

4. Dogs treated with proper amounts of SBI following the induction of pancreatitis showed a rapid return of blood pressure to normal levels. The proteolytic activity and antiproteolytic activity were maintained at normal levels. In one dog the antiproteolytic activity of the serum was increased. The one dog in this group followed for more than 12 hours showed a marked but only transient clinical improvement compared to dogs untreated with SBI.

5. SBI exerted a powerful anticoagulant effect lasting several hours on the blood of dogs.

6. Elevation of proteolytic activity in the serum of dogs appears to be a principal factor in the initial shock of acute pancreatitis.

7. SBI apparently is capable of specifically counteracting the elevation of proteolytic activity and the shock found in acute pancreatitis in dogs. It may have considerable potential value in the clinical treatment of the shock of acute hemorrhagic pancreatitis, but further extensive experimental trial is required.

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EFFECT OF SIMULTANEOUS ORAL ADMINISTRATION OF AUREOMYCIN AND ALUMINUM HYDROXIDE GEL ON FECAL UROBILINOGEN

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AUREOMYCIN, in addition to being an antimicrobial agent, has many effects on the host. Sborov, Jay, and Watson,[1] and Galt and Hunter[2] observed that the oral administration of aureomycin caused a marked decrease in the concentration of fecal urobilinogen. Lichtman and co-workers[3] reported that a reticulocyte response followed oral aureomycin therapy in patients with pernicious anemia. The finding of Macht and Farkas[4] that aureomycin increased the coagulability of the blood has been confirmed by some workers and denied by others.[5-7] A growth factor in aureomycin that is distinct from vitamin B_{12} has been reported by Stokstad and co-workers.[8] Photosensitization, acute vitamin deficiencies, and decreased blood coagulability are other systemic effects of aureomycin that have been observed.[2, 9, 10] In each of these phenomena the question arises whether the result is due directly to the aureomycin or whether it is due to the effect of aureomycin on the bacterial flora of the bowel.

Aluminum hydroxide gel administered concurrently with aureomycin markedly decreases the absorption of the drug from the gastrointestinal tract.[11-15] This finding suggested a possible means of separating the direct from the indirect effects of aureomycin. If aluminum hydroxide gel prevented absorption of aureomycin into the blood stream without inhibiting its antibacterial activity in the intestinal tract, a convenient tool for studying phenomena due solely to the effect of aureomycin on the bacterial flora of the bowel would be available. In addition, aluminum hydroxide gel might increase the efficacy of aureomycin as an intestinal antiseptic by concentrating it within the lumen of the bowel. Since the urobilinogen in the feces is produced by bacteria in the bowel, the amount present must be related to the number of viable organisms. Thus if the simultaneous administration of aureomycin and aluminum hydroxide gel resulted in a significant lowering of the fecal urobilinogen it could be presumed that the aureomycin had reduced the number of bacteria in the bowel in spite of the fact that it had not been absorbed.

The following study presents the effect of the concurrent administration of aluminum hydroxide gel and aureomycin on the production of urobilinogen by the bacteria of the bowel. The bactericidal activity of mixtures of aureomycin and aluminum hydroxide gel also was determined.

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MATERIALS AND METHOD

Five female patients without demonstrable gastrointestinal or liver disease were given 0.5 Gm. of aureomycin* with 15 ml. of aluminum hydroxide gel† orally every 6 hours for 6 to 7 days. Prior to the administration of the drugs, control specimens of feces from each patient were analyzed for Ehrlich's units

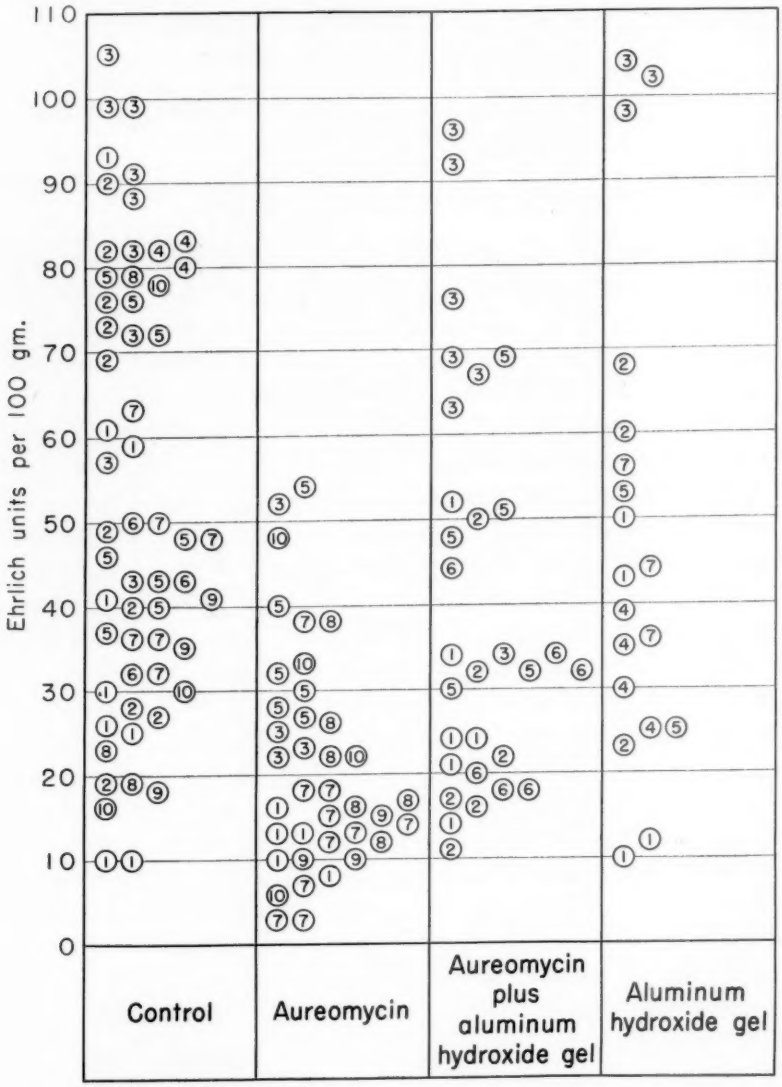

Fig. 1.—Effect of simultaneous administration of aluminum hydroxide gel and aureomycin on fecal urobilinogen. Each circle represents one determination. The number inside the circle indicates the number of the patient. The drugs were administered in the following order: (1) aluminum hydroxide gel, (2) aureomycin with aluminum hydroxide gel, (3) aureomycin alone. An analysis of variance‡ revealed a statistically significant difference (P-value = $< .01$) between the control values and those after aureomycin. There was not a statistically significant difference between the control values and those obtained after aluminum hydroxide alone (P-value = > 0.1), or after aluminum hydroxide and aureomycin together (P-value = > 0.1).

*Supplied by Lederle Laboratories, Division of American Cyanamid Co., New York.

†Wyeth Incorporated, Philadelphia.

‡Performed by Dr. D. Simmons, using the methods outlined in *Sampling Statistics and Applications*, by Smith and Duncan, 1945.

by the method of Watson.[16] Daily fecal Ehrlich determinations were done on 10 Gm. aliquots during the course of therapy. Additional control data as to the effect of aluminum hydroxide gel alone and aureomycin alone on fecal urobilinogen concentration were gathered from 5 other female patients. The concentration of aureomycin in the blood of some of the patients was determined by the method of Dornbush.[17] The in vitro activity of mixtures of aureomycin and aluminum hydroxide gel was determined by adding 0.5 ml. of a 1:100 dilution of dextrose broth of an 18 hour growth of *Bacillus cereus* to 2 rows of tubes; one containing decreasing concentrations of aureomycin dissolved in aluminum hydroxide gel and the other the same concentrations of aureomycin in 0.9 per cent NaCl. After 18 hours at 37° C., 0.1 ml. aliquots from each series of tubes were placed in 10 ml. of dextrose broth. They were then incubated at 37° C. for 48 hours. The bactericidal end point of this test was indicated by the tubes in which no growth occurred.

RESULTS

When administered with aluminum hydroxide gel, aureomycin did not cause a significant fall in the concentration of urobilinogen in the feces (Fig. 1). When only aluminum hydroxide gel was given, there was not a significant effect on the urobilinogen values (Fig. 1). On the other hand, the data confirm previous observations[1, 2] that the administration of aureomycin alone caused a decrease in fecal urobilinogen (Fig. 1). The blood concentration of aureomycin fell when aluminum hydroxide gel was administered as in previous experiments.[9]

The in vitro study of the bactericidal activity of aureomycin in the presence of a suspension of aluminum hydroxide gel revealed that the mixture was inactive. Although concentrations of 0.15 μg per 1 ml. aureomycin killed the *Bacillus cereus* in saline, when aluminum hydroxide gel was present, the organism grew in a concentration of 2.5 μg per 1 ml. aureomycin.

DISCUSSION

These results indicate that when aluminum hydroxide gel is administered concurrently with aureomycin the latter drug does not have its usual effect on the bacterial flora of the gastrointestinal tract. This is further substantiated by the fact that suspensions of aluminum hydroxide gel inactivate aureomycin in vitro. Consequently the administration of these drugs together will not help to separate the systemic effects of aureomycin from those due to its action on the flora of the colon. An investigation of the effect on urobilinogen production of aureomycin administered intravenously might provide useful information in this respect. The present results also suggest that aluminum hydroxide gel should not be given concurrently with aureomycin even in cases in which the sole object is an antibacterial effect within the gastrointestinal tract.

SUMMARY

When aluminum hydroxide gel was given concurrently with aureomycin the latter drug did not cause a significant fall in the concentration of urobilinogen in the feces. In vitro, aluminum hydroxide gel suspensions markedly de-

creased the bactericidal activity of aureomycin. Thus, aluminum hydroxide gel not only decreased the absorption of aureomycin into the blood stream, but also inactivated it within the gastrointestinal tract.

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THE PROPHYLACTIC USE OF TERRAMYCIN IN EXPERIMENTAL CLOSTRIDIUM WELCHII INFECTION IN GUINEA PIGS

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THIS is a report of laboratory experiments which were conducted to determine the value of the antibiotic, terramycin,[1] as a prophylactic agent for an experimental *Clostridium welchii* infection in guinea pigs, simulating gas gangrene in the human being. The method used is that previously described for the appraisal of other antibiotics in clostridial infection.[2, 3]

The study was conducted so that in each experiment one group of control animals received a wound and a contaminating inoculum of *Cl. welchii* but was given no terramycin, while another group of animals comparable in number and in weight received a wound, an identical contaminating inoculum, and terramycin.

The animals were anesthetized with sodium pentobarbital and operated upon under aseptic technique. The gluteus maximus muscle was exposed through a skin incision and a portion of it was traumatized by crushing with a clamp. The incision was closed with sutures and sealed with collodion. Finally the wound was contaminated by injection of 0.1 c.c. of a 5 to 10 hour culture of *Cl. welchii* through the adjacent normal skin into the traumatized muscle using a needle and syringe. A monosodium salt of terramycin* prepared from terramycin base was used as the prophylactic agent. A solution of the drug was injected into the muscle of the leg opposite to the one traumatized and contaminated, within 10 minutes after operation. Only a single injection was administered. The dosage is expressed in terms of milligrams of terramycin base per kilogram of the animal's body weight. It ranged from 0.5 to 100 mg. per kilogram. Every animal that died was subjected to a post-mortem examination. All surviving animals were kept under observation for 7 days, then sacrificed and autopsied. The results of these experiments are shown in Table I.

Not included in these statistics are 6 animals that received terramycin and that developed conjunctivitis and nasal discharge and died before the end of the 7 day period of observation. At post mortem examination, pulmonary consolidation in varying degrees was present but there was no evidence of clostridial infection.

All of the animals in the control group (i.e., those that received the contaminating inoculum but no terramycin) developed an infection which simulated clinical gas gangrene in the human being. Of these, 85 per cent died, while 15 per cent survived the 7 day period of observation.

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*The terramycin used in these experiments was supplied by Chas. Pfizer and Co., Inc., Brooklyn, N. Y.

TABLE I. EFFECT OF A SINGLE INTRAMUSCULAR INJECTION OF TERRAMYCIN IN THE PREVENTION OF EXPERIMENTAL CL. WELCHII INFECTION IN GUINEA PIGS

AMOUNT OF TERRAMYCIN	0	0.5 TO 2 MG. PER KG.	3 TO 100 MG. PER KG.
Total number of animals	75	29	85
Survived 7 day observation period; no evidence of clostridial infection	0%	55%	100%
Developed clostridial infection but survived observation period	15%	45%	0%
Died of clostridial infection	85%	0%	0%

The animals which received a single intramuscular injection of terramycin in the amount of 3 mg. or more per kilogram were protected from *Cl. welchii* infection. Of the animals that received less than the 3 mg. dosage, 45 per cent developed swelling, often accompanied by crepitation, of the wounded extremity within the first 48 hours following contamination. In each instance the process resolved. At the end of the 7 day period of observation, when these animals were sacrificed and autopsied, there was no gross evidence of clostridial infection.

CONCLUSIONS

The results of these experiments indicate that the antibiotic, terramycin, protects guinea pigs from *Cl. welchii* infection when a single intramuscular injection of 3 mg. or more per kilogram is administered in the contralateral leg within 10 minutes following contamination.

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FIBROTIC STENOSIS OF THE TERMINAL COMMON DUCT

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FOR many years, surgeons have been reluctant to operate upon the gall bladder in patients in whom the cholecystogram was normal. The percentage of overlooked calculi in such a radiographic examination was small, especially if the examination was repeated. When a patient with a stoneless gall bladder was operated upon, Homans advocated a search for unsuspected lesions, if evidence of only trifling disease of the organ was discovered. Many authors have called attention to the numerous therapeutic failures which have followed the removal of gall bladders which did not contain calculi. In a careful follow-up of 102 such cases, Whipple found only 65 per cent free of symptoms for one year or longer. Maingot stated that in his experience less than 25 per cent were symptom-free after operation.

The clinical history of the patient, however, is often of more value than the x-ray examination. Walters stated that he had removed innumerable diseased gall bladders which had filled and emptied normally according to routine x-ray examination, and in which stones had not been seen. He likewise mentioned the removal of fifteen large common duct stones from patients whose gall bladders had functioned normally and who had not been jaundiced. Doubilet and Mulholland stressed the importance of spasm of the sphincter of Oddi in occluding the lower end of the common duct, thus producing biliary symptoms. Recently, Trommald and Seabrook called attention to benign fibrosis of the sphincter of Oddi as a cause of obstruction of the terminal common duct. They discovered the condition by observing a persistent narrowing of the sphincter on postoperative cholangiograms or by finding it impossible to pass a dilator through the sphincter at the time of common duct exploration.

The purpose of this paper is to describe a group of three patients with marked symptoms of biliary tract disease in spite of normal filling and emptying of gall bladders which did not contain calculi at the time of standard cholecystography. X-ray visualization of an obstructed common duct at the time of the evacuation type of cholecystography provided the basis for exploring this group of patients (Sachs).

DIAGNOSIS

As pointed out by Trommald and Seabrook, fibrotic stenosis of the terminal common duct occurs in older people, the average age in the present group being 54 years. All three patients had histories of several years duration of epigastric and right upper quadrant sharp pain which occasionally radiated to the back

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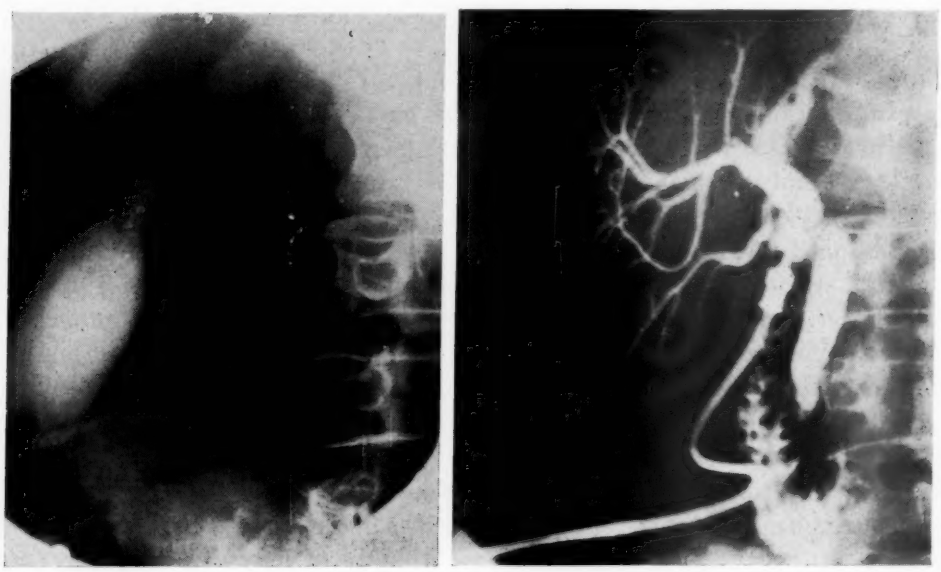
and which was associated with nausea and vomiting. In two of the patients, typical attacks of pain could be produced by injections of morphine. As a result of the unexplained nature of their symptoms, all three patients were considered to be psychoneurotic. None of the group had been jaundiced, but weight loss up to a maximum of 45 pounds was a prominent symptom in two cases.

Laboratory findings were not distinctive. The icteric index, serum amylase, cephalin flocculation, and thymol turbidity determinations were normal. X-ray examination of the intestinal tract including barium enema and gastrointestinal series was normal in all patients. Oral cholecystograms revealed gall bladders which filled, emptied with some delay, and contained no stones. The common ducts were slightly dilated and terminated with abrupt narrowing in the region of the sphincter of Oddi (Fig. 1, *A*). In two cases, various antispasmodics including atropine, amyl nitrite, and nitroglycerine were administered without affecting this narrowing. All three patients were considered to have partial obstruction of the terminal common duct in the region of the sphincter of Oddi.



A. *B.*

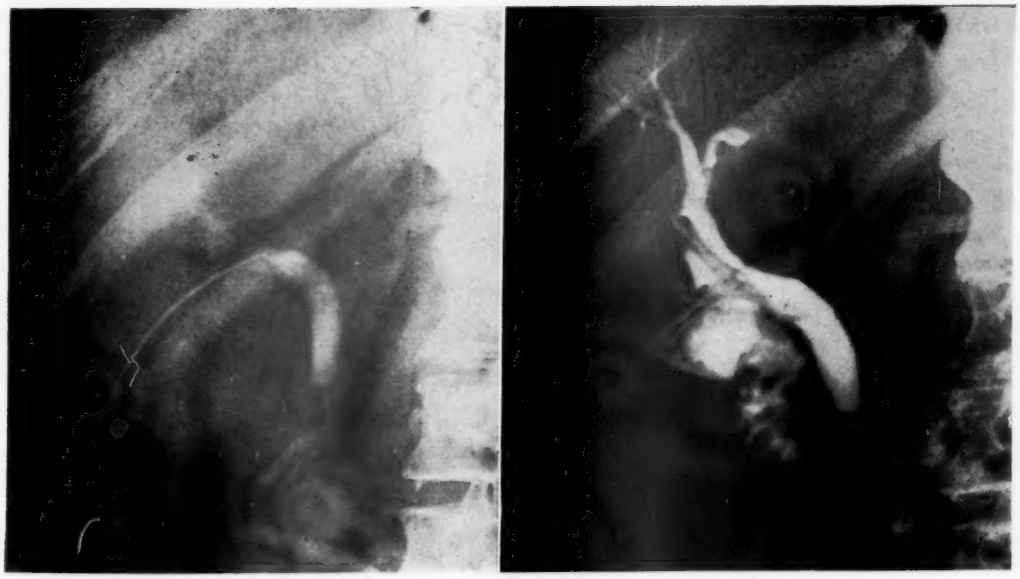
Fig. 1.—C. K., 52-year-old white man with a two and one-half year history of severe, intermittent, right upper quadrant pain, associated with vomiting and a 45 pound weight loss. No history of jaundice. Gastrointestinal roentgenograms were normal. *A*, Evacuation type of oral cholecystogram showing dilated common duct ending in an abrupt taper with no dye in the duodenum. *B*, Operative cholangiogram confirming dilated common duct ending in abrupt taper with narrowing of sphincter of Oddi.

OPERATION

Operations were carried out under intratracheal gas-oxygen-ether anesthesia. The gall bladder appeared normal grossly in two cases and was somewhat thickened in the third. In all three, operative cholangiograms confirmed the preoperative diagnosis of partial obstruction of the terminal common duct (Fig. 1, *B*). In one case, because of a partial relaxation of the sphincter of Oddi in response to amyl nitrite preoperatively, the common duct was drained and the

gall bladder removed. Microscopic examination of the gall bladder showed cholesterosis. After three months of drainge by means of a T tube, there was still marked narrowing in the region of the sphincter of Oddi, and pain was produced by clamping the T tube (Fig. 2, *A-D*). Transduodenal exploration

A. *B.*



C. *D.*

Fig. 2.—P. P., 57-year-old white man with a two-year history of epigastric pain radiating to both upper quadrants, associated with marked anorexia and a 20 pound weight loss. No history of jaundice. Gastrointestinal roentgenograms and barium enema were normal. *A*, Operative cholangiogram showing dilated common duct with narrowing of the sphincter of Oddi. *B*, Postoperative cholangiogram (one month) showing dilated common duct with abrupt cut-off at sphincter of Oddi. *C*, Postoperative cholangiogram (two months) showing dilated common duct with narrowing of the sphincter of Oddi. *D*, Postoperative cholangiogram (three months) showing dilated common duct with cut-off at the sphincter of Oddi.

of the sphincter revealed it to be a firm cylinder of tissue measuring roughly 2 cm. by 0.5 cm. with a lumen which would admit only a probe. On section of the sphincter, its walls were firm, grayish white, and approximately 2.5 mm. thick.

Both of the remaining cases had duodenal scarring suggestive of inactive duodenal ulcers in spite of normal gastrointestinal roentgenograms. Neither showed relaxation of the narrowing of the terminal common duct, either in response to the nitrites or to the injection of 1 per cent procaine at the angulus of the stomach to block the vagus innervation of the sphincter of Oddi (Mallet-Guy). During combined supraduodenal and transduodenal common duct explorations, it was impossible to pass a No. 10 French catheter into the duodenum in one case. Only the tip of a bougie passed through the sphincter in the other. Ureteral catheters could be passed, and served as guides to the papilla of Vater. In both patients, the sphincters of Oddi were cut through their superior borders over a grooved director or catheter (Fig. 3). The incision was extended until

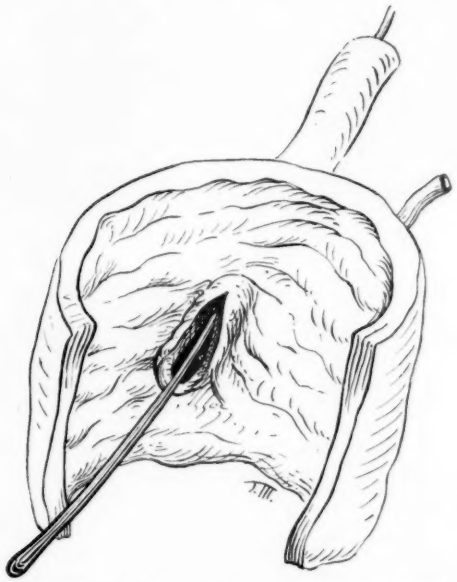


Fig. 3.—Diagram showing stenotic and thickened sphincter of Oddi sectioned over a catheter.

the lumen of the sphincter was adequate to draw a No. 16 French, long-arm T tube into the duodenum easily. The length of this incision varied from 1 cm. to almost 2 cm. Biopsies taken at the time of sphincterotomy showed increased fibrous connective tissue in the sphincter muscle with considerable increase in over-all thickness. Both gall bladders were removed in spite of their normal appearance. There is some evidence from pressure determinations in various parts of the biliary tract that a competent sphincter of Oddi is essential for the normal functioning of the gall bladder. It is likewise impossible to be certain of the absence of chronic inflammation of the gall bladder by inspection alone. On microscopic examination, both gall bladders were thin-walled and normal without increased fibrous connective tissue or round-cell infiltration. The pathologic diagnosis in both was "normal gall bladder."

RESULTS

The postoperative course of the patient whose sphincter was cut at a second operation was complicated by a subphrenic collection of bile and a wound abscess. This may have been associated with a preoperative bile culture of *Aerobacter aerogenes* and *Bacillus pyocyaneus*. In spite of these difficulties, the amount of bile drainage decreased rapidly. The long-arm T tube was removed in three weeks, and the sinus healed rapidly. The other two patients had uncomplicated postoperative courses. Their long-arm T tubes were removed three months after operation, and both sinus tracts healed promptly. There was a moderate amount of drainage of duodenal contents through the T tubes in all three cases without irritation of the skin at the wound edges and without cholangitis. In one patient, the removal of the T tube was associated with chills and fever for twenty-four hours.

All three patients have been relieved of their attacks of severe right upper quadrant pain. Only one is asymptomatic, however, and the follow-up period has been short (longest, 18 months). One patient is troubled with abdominal discomfort related to a small incisional hernia which developed following his wound abscess. Another has had a subsequent hospital admission for burning epigastric distress which was relieved by food or Amphojel. She was discharged greatly improved symptomatically by the use of Banthine. Jaundice and acholic stools have not been noted postoperatively in the group. All patients have gained some weight. It is doubtful whether two of the patients will ever be entirely free of symptoms due to confirmed psychoneuroses.

DISCUSSION

As Cattell has stated, more and more cases are being found in which the entrance of the common bile duct into the duodenum is diminished in size by spasm or fibrosis. It is important to institute adequate treatment in such cases if recurrent symptoms are to be avoided. Failure to do so accounts for the majority of cases of the postcholecystectomy syndrome which are not due to retained calculi.

It is interesting to speculate as to the causes of fibrosis of the sphincter of Oddi. Trommald and Seabrook have suggested that the thickening of the sphincter may have been part of a general common duct thickening associated with chronic cholangitis. The narrowing of the duct, however, seems sharply limited to the region of the sphincter with some proximal common duct enlargement. At the time of sphincterotomy, the limit of the thickened sphincter is usually apparent. Some of the scarring of the sphincter may be due to the spontaneous passage of stones or, as shown by Zollinger, Branch, and Bailey, to instrumental dilation of the sphincter. It is difficult to postulate such a mechanism in the present group of patients in whom calculi and previous surgery were not factors. An area of localized pancreatitis sometimes produces an inflammatory stricture of the sphincter of Oddi. Normal serum amylase determinations, as in the series discussed here does not preclude this possibility, as the process had long since ceased to be acute.

Doubilet and Colp demonstrated that the instillation of 0.9 per cent hydrochloric acid into the duodenum opposite the papilla of Vater would produce marked spasm of the sphincter of Oddi with a rise in intraductal pressure. During post-mortem examination of several cases of cholecystitis and associated peptic ulcer, Giordano and Mann noted that there was a definite hypertrophy of the muscle bundles about the terminal common duct with thickening of the wall of the sphincter up to 2 mm. It is possible that in patients with duodenal ulcer, production of spasm by excess hydrochloric acid for a prolonged enough period of time might account for the fibrosis of the sphincter. This may have been the etiologic mechanism in two of the cases under discussion.

On the basis of animal experimentation, Trommald and Seabrook felt that a divided sphincter of Oddi remained incompetent permanently. Cattell and others have stressed the importance of leaving a long-armed T tube through the divided sphincter for a period of six months. No demonstrable difference was apparent between the case in which the T tube was removed after three weeks and the ones in which it remained in place for three months. The period of follow-up on the cases presented is much too short for valid conclusions concerning therapeutic results.

SUMMARY

The patient with a stoneless, functioning gall bladder has always been considered a very poor candidate for biliary surgery in spite of apparently genuine symptoms of gall bladder disease. In some such patients, it is possible to demonstrate a dilated common duct with narrowing of the sphincter of Oddi by the evacuation type of oral cholecystogram. Combined supraduodenal and transduodenal exploration reveal a sphincter of Oddi which will allow the passage of only a fine probe. Biopsy of the sphincter at the time of sectioning reveals increased fibrous connective tissue. Peptic ulcer may be an associated condition of possible etiologic significance in the formation of fibrosis of the sphincter of Oddi.

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THE OCCURRENCE IN SURGICAL PATIENTS OF SEVERE HYPERNATREMIA WITHOUT EXOGENOUS DEHYDRATION

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THERE are in the literature occasional reports of severe hyperconcentration of electrolytes occurring in patients who have not been deprived of fluid and in whom dehydration, in the usual sense, is not present. In some instances renal damage has occurred either from the toxic action of drugs or from other forms of insult to the kidneys.[1, 2] In others, the disorder has been related to central nervous system damage resulting in functional renal impairment.[3-5] In the former group of cases, secondary changes in the brain have been demonstrated. In both types of cases, there appears to be a pathologic selective secretion of water with retention of sodium and chloride despite the mounting levels of these ions in the plasma.

In this paper, five cases are presented in which rather detailed measurements of intake and output and serum electrolyte data are available and in some of which higher sodium concentrations were found than have been previously reported. The pathogenesis of the syndrome in these cases is not clear. They serve, however, to illustrate some of the clinical manifestations of this state as well as the variety of circumstances under which it might be expected to occur. The dire nature of the clinical pictures, and the fact that four of the five patients died, argue for the importance of early recognition of hypernatremia and for the necessity of further investigation of the factors underlying a pathologic increase in serum sodium level.

CASE 1 (U. H. No. 828159).—B. B., a 54-year-old woman, was admitted with a history of diarrhea following drainage of a rectal abscess two weeks prior to admission. She had been well up to this time except for anorexia and a 30 pound weight loss during the year before admission. The past history included an episode of diarrhea about 15 years previously which lasted for one year and subsided without specific therapy. Physical examination revealed evidence of recent weight loss. There were changes in the tongue and buccal mucosa suggestive of nutritional deficiency. Heart and lungs were normal. The abdomen was distended slightly and intestinal sounds were somewhat increased in activity. No masses were felt nor tenderness elicited. On digital examination of the rectum a firm tender inflammatory stricture was felt which exuded pus. Sigmoidoscopy under anesthesia revealed extensive changes characteristic of ulcerative colitis above the area of the inflammatory stricture.

Course.—The patient was placed on Banthine, 100 mg. every six hours, and a high calorie diet which she took poorly. Because of inadequate oral intake it was necessary to supplement the fluid intake with intravenous solutions. On the third hospital day, the

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temperature rose to 101.8° F. and continued to exhibit daily spikes of 101° to 102° F. She had been afebrile on admission. Penicillin, 600,000 units daily, was begun along with chloromycetin, which was given in doses of 1.5 Gm. daily for five days. On the seventh hospital day, terramycin was started, but was abandoned after three days because of the patient's poor cooperation in taking medicine by mouth.

She continued to have diarrhea and became incontinent of both urine and feces. The output of liquid stools ranged from 100 c.c. to 750 c.c. daily. Intravenous fluids were given in amounts believed to be adequate to cover losses from this source as well as normal daily requirements (Table I). Though blood chemical values had been essentially normal at the time of admission, on the tenth hospital day, the picture of dehydration with hyperchloremia and hypernatremia was first observed. This occurred despite what appeared to be adequate intakes of fluid and rather large urine outputs. With the finding of high sodium values and low serum concentrations of potassium, larger amounts of fluid (glucose solution) were administered containing little or no sodium chloride and rather large amounts of potassium. This therapy, though it raised the potassium level somewhat, had little effect on the picture of extracellular dehydration which persisted up to the time of the patient's death.

TABLE I (CASE 1). INTAKE AND OUTPUT, BODY WEIGHT, AND CHEMICAL STUDIES

HOSPITAL DAYS:	10	11	12	13	14	15	16	17	18	19
Intake H_2O (c.c.)	4,250	3,770	4,300	3,000	3,290	3,845	5,200	3,000	5,500	
NaCl (Gm.)	9	4.5			4.5	4.5	4.5	4.5	4.5	
KCl (Gm.)				8	4	2	4	8	8	
Output urine (c.c.)	700	2,150	3,550	1,000	1,100	1,200	1,850	2,250	2,080	
Diarrhea (c.c.)	95	200	500					185		
Hemoglobin (Gm. %)	16.3	16.5	15.8		14.6			14.8	13.5	
Chloride (meq./L)	114		125		110	108	99	113	125–128	115
CO_2 combining power (meq./L)	28		28		28	29	25	25	25–23	24
Sodium (meq./L)			168					165	165–163	155
Potassium (meq./L)			2.2					2.7	3.1	3.5
BUN (mg. %)							7	4	5	5
Protein (Gm. %)	8.2							5.4		
Urine										
Specific gravity	1.006									1.012
Glucose	1+									
Albumin	1+									
Urine chloride										27 meq./L
Sediment	Occ.	R.B.C.								
	4+	W.B.C.								
Body weight (kg.)	45.2	45.7	45.0	44.2	43.6	43.4	42.4	44.5	44.6	45.9
Weight on admission (kg.)	45.0									

On the sixteenth day, the patient became unaware of her surroundings, and later in the day developed a generalized seizure with jacksonian progression beginning in the right upper and lower extremities and with deviation of the eyes to the right. She lapsed into profound coma from which she never recovered, and died on the twentieth day after admission.

An autopsy showed severe changes of chronic ulcerative colitis, fatty metamorphosis of the liver and chronic cholecystitis. There was encephalomalacia due to hemorrhage involving the left cerebellar hemisphere and posterior inferior temporal lobe. Examination of the kidneys showed minimal changes of hydronephrosis bilaterally. There were some hydropic changes in the epithelium of the proximal convoluted tubules, dilation of some of the proximal tubules, and occasional amorphous, hyaline casts occupying the distal convoluted tubules.

Chemical and Other Laboratory Data.—Table I shows the values of fluid intake and output, the body weight, and laboratory data from the tenth hospital day, prior to which the chemical values had been within normal limits.

The chemical picture of dehydration was first observed on the tenth hospital day and was maximal on the twelfth day with the sodium value of 168 meq. per liter. The potassium was low (2.2 meq. per liter on the twelfth day) and the electrocardiogram gave confirmatory evidence of hypokalemia. That this hyperconcentration of electrolytes developing between the second and tenth days was not due merely to an excess loss of water is borne out by the relative constancy of the body weight during that period. The hyperchloremia and hypernatremia remained essentially unchanged for the remainder of the patient's life, despite the administration of rather large amounts of fluid and very small qnantities of salt. Urinary output measurements were inaccurate during the first 10 days of the hospital period but appeared to be adequate (700 c.c. to 3,550 c.c.) following the establishment of quantitative collection with an inlying catheter. It is of interest to note the relatively low urinary specific gravities which were recorded despite the apparently high degree of concentration of the plasma.

CASE 2 (U. H. No. 825455).—H. B., a 64-year-old man, was admitted for treatment of a squamous-cell carcinoma of the left ear with cervical node metastases. He was in good condition and there was no evidence of pre-existing metabolic disease. On the third day after admission an excision of the ear was carried out together with a radical dissection of the cervical lymph nodes. The immediate response to the procedure was good and the patient was up and walking by the second day after operation. The fluid intake was maintained at first by intravenous solution and later by nasogastric tube feedings. The daily output of urine was satisfactory.

The patient continued to do well until the sixth day after the procedure, when the temperature rose to 103° F., the pulse became rapid and weak, and blood pressure dropped to 88 systolic. The patient became disoriented and made continual restless grasping movements in the air and at objects around him. There were twitching movements of the facial and peripheral muscles. The skin became cold and mottled. At this time the extraordinary electrolyte pattern described later was first observed. No reason for the fever, tachycardia, and mental confusion was apparent. An electrocardiogram was considered suggestive of coronary insufficiency.

With the finding of extremely elevated electrolyte concentrations (chlorides 146 meq. per liter; sodium 196 meq. per liter) large amounts of fluids were given intravenously consisting mostly of 5 per cent glucose solution. Despite the daily administration of 2,400 to 5,000 c.c. of fluid, however, it required 10 days to return these concentrations to normal levels. Fever and tachycardia subsided within 2 days, but the mental confusion persisted, gradually improving over a period of 12 to 13 days. The patient went on to a satisfactory recovery.

Blood Chemistry and Other Laboratory Studies.—Table II contains a portion of the intake and output data together with the laboratory findings for the sixth to eighteenth days after operation. It will be noticed that in this case, the blood urea nitrogen was severely elevated, reaching 145 on the tenth postoperative day. The correlation of the degree of uremia with the electrolyte concentrations seems to indicate that the disturbance responsible for the latter was primarily a renal one. Although 3 kilograms of body weight were lost in the 6 days between operation and the first measurement of the electrolyte values, it seems unlikely that water deprivation could have been responsible for the picture of uremia and hyperconcentration. Uremia of this degree is not likely to occur on an extrarenal basis, particularly in the face of the output of relatively large amounts of urine without high specific gravity. It would appear rather that a selective excretion of water with retention of electrolytes had taken place. As might be expected, the weight was partially regained when the electrolytes became diluted to their normal concentrations.

Five months after his discharge from the hospital, this man was readmitted with severe abdominal symptoms which he had not exhibited previously and which were not related to the condition for which he had originally been treated. He was vomiting and dehydrated on this admission. He died and at autopsy was found to have a large carcinoma of the pancreas involving the entire upper abdomen with metastases of the liver,

lungs, and brain. The kidneys were grossly normal but on microscopic examination, some atrophic changees were seen in the renal tubular epithelium, suggestive of recent damage. In addition there was round-cell interstitial infiltration and giant cells and mitotic figures were to be found in the tubular epithelium. These were felt to be indicative of regenerative changes in damaged tubules.

TABLE II (CASE 2). INTAKE AND OUTPUT, BODY WEIGHT, AND CHEMICAL STUDIES

POSTOPERATIVE DAYS:	6	7	8	9	10	12	13	14	18
Intake (c.c.) oral and IV	3,000	2,800	3,300	3,720	2,390	3,500	3,500	3,500	3,700
NaCl (Gm.)								4.5	4.5
KCl (Gm.)				3				5	
Output urine (c.c.)	1,450	1,000+	810	1,400	2,000	1,200	1,200	1,300	2,000
Hemoglobin (Gm. %)		15.6		13.5			11.2		
Chloride (meq./L)		146	140	127	125	127	130	122	104
CO_2 combining power (meq./L)		18	24		21	14	18	16	26
Sodium (meq./L)			196	190	164	160	157	151	138
Potassium (meq.L/)			5.4	5.4	5.5	5.5	4.6	4.0	5.2
BUN (mg. %)	41	138	130	132	145	75	53	50	19
Creatinine (mg. %)	1.2		3.5	3.35	3.3	2.4	2.1	1.7	
Protein (Gm. %)				7.1		6.0			4.6
Urine									
Specific gravity			1.023	1.017	1.014	1.018	1.018	1.017	1.014
Glucose			2+						
Albumin			1+		Trace				
Sediment			Coarse granular cast		Occ. R.B.C. Occ. W.B.C.				
Body weight (kg.)	67.3	66		64.5	65.3	64.5	64.2	64.5	66.8
Preop. weight (kg.)	69.0								

CASE 3. (U. H. No. 816480).—H. W., a 66-year-old man, underwent a subtotal gastrectomy for a duodenal ulcer which had been present for 20 years. A cholecystectomy and an appendectomy were done at the same time. He was discharged from the hospital 16 days after operation but readmitted one month later because of anorexia, poorly defined abdominal pain, profound weight loss, and malnutrition. This picture was felt to be largely one of hypochondriasis and the patient manifested depression and other varieties of psychotic behavior which seemed to substantiate this diagnosis. However, daily fever of 101° to 102° F. was noted and this, along with his abdominal symptoms, prompted an exploration in an attempt to find an intraperitoneal abscess. No such abscess was found. The fever gradually subsided, however, on therapy with penicillin and aureomycin and the patient was almost afebrile after about the fortieth hospital day. Since the nutritional problem persisted, the patient required maintenance on daily intravenous fluids and, for periods, nasogastric instillation of milk and similar materials.

On the sixty-fifth day after readmission, the temperature suddenly rose to 103° F. and the patient became comatose. At this time the electrolyte picture of hyperchloremia and hypernatremia was first observed (*vide infra*). He remained unresponsive for the remainder of his life, exhibiting bizarre athetoid and grasping movements and muscular twitching. He died 17 days after this acute episode. Permission for an autopsy was not granted.

Blood Chemistry and Other Laboratory Data.—Table III contains excerpts from the intake-output data and laboratory findings on this patient, showing the values on admission and on representative days thereafter. During the first two months after admission, oral intakes were supplemented by intravenous feeding to the extent that urine outputs of 1,500 to 3,000 c.c. were achieved. After this, intravenous feedings were not given; this resulted in a considerably reduced intake and daily outputs of less than 1,000 c.c., and apparently a considerable degree of dehydration which reached its maximum severity on the sixty-

fifth hospital day. On this day the body weight was 10 kilograms below the admission weight, and the high fever and coma appeared suddenly. The extraordinary hyperconcentration of electrolytes with serum sodium level of 196 meq. per liter and chloride of 121 meq. per liter was first observed on that day.

In this instance the picture of acute hyperconcentration was apparently precipitated by a period of relative fluid deprivation and consequent dehydration. The presence of an underlying renal defect is indicated, however, by the fact that the urine specific gravity was only 1.009 at the time the electrolyte distortion was maximal. Furthermore, the blood urea nitrogen, which had risen to 67 mg. per cent at this time, continued to rise in subsequent days even though the electrolyte picture of dehydration was rapidly restored to normal by large amounts of intravenous fluid. The central nervous system damage was not reversible, since the coma and bizarre neurological finding persisted until death.

TABLE III (CASE 3). INTAKE AND OUTPUT, BODY WEIGHT, AND CHEMICAL STUDIES

HOSPITAL DAYS:	2	8	14	32	39	67	69
Intake (c.c.)							
oral and IV	3,500	4,150	3,300	3,500	4,850	4,000	3,000
NaCl Gm.	2		2	4.5	8		
KCl Gm.					2		
Blood (c.c.)					500		
Output c.c. urine		3,000	1,800	800	2,300	40	400
Hemoglobin (Gm. %)	13.6	12.3	14	13.5	12.6	15.6	
Chloride (meq./L)	103	115	94	115	99	121	93
CO_2 combining power (meq./L)	25	20	28	30	33	34	25
Sodium (meq./L)			142			196	145
Potassium (meq./L)			3.1			2.8	2.8
BUN (mg. %)	20	62	19	27		67	92
Creatinine (Gm. %)						4.6	
Protein (Gm. %)	7.4	5.3	4.7				
Urine							
Specific gravity	1.008	1.010	1.010	1.014	1.001	1.009	
Albumin						1+	
Sediment	Fine granular casts 1+ W.B.C.	3+ W.B.C.				4+ W.B.C.	
Body weight (kg.)	48.0		53.0	46.6	49.8		39.0

CASE 4 (U. H. No. 829327).—J. T., a 67-year-old man, was admitted on the urological service in acute urinary retention. Details of the past history were not obtainable, but it was known that he had had diabetes for about 15 years and hypertension for about 10 years. He was somewhat stuporous, but responsive at the time of admission. Temperature was normal, pulse 110, and blood pressure 190/100. A spinal puncture revealed nothing of note. Inlying catheter drainage resulted in a urine output of 6,400 c.c. in the first day. Intravenous fluids were given. Fluids consisted entirely of 5 per cent glucose solution and, except for 2 Gm. of KCl on the fourth day, no intravenous electrolytes were given. There was a considerable improvement during the first 24 hours, so that by the next day he was fully conscious, talking normally and answering questions. However, on the third hospital day the temperature, which had been normal on admission, rose to 102° F., and his mental state began to deteriorate again. He became gradually less responsive, progressed into coma, and died on the seventh hospital day. The fever had remained elevated, reaching 106° F. on the day of death. He received penicillin, aureomycin, and streptomycin during the period of his hospital stay.

An autopsy revealed arteriosclerosis involving the cerebral, coronary, and renal vessels. There was encephalomalacia involving the right internal capsule and small post-encephalomalacic cysts in the basal nuclei and two small cysts in the pons and right dentate nucleus. These were felt to be old lesions, probably not related to the cause of

death. There was some bronchopneumonia involving the right middle and lower lobes. There was a carcinoma of the prostate without evidence of metastases. Microscopic examination of the kidneys disclosed sclerosis of large and small vessels. There was interstitial infiltration composed of round cells and a large number of eosinophils. There was fine vacuolation of the tubular epithelial cytoplasm particularly marked in the proximal convoluted tubules.

Laboratory and Chemical Findings.—Table IV shows what intake and output data are available along with the serum electrolytes and other laboratory findings. On admission the blood urea nitrogen was 135 mg. per cent, the CO_2 combining power 15 meq. per liter, and the chloride 104 meq. per liter. With the onset of diuresis and the institution of intravenous treatment, the blood urea nitrogen rapidly fell and the acidotic values of the CO_2 combining power returned to normal. The chlorides rose to very high levels, as did the sodium which reached 172 meq. per liter on the day before death. It is apparent that this man was excreting large amounts of urine without salt and thereby concentrating electrolytes to an extraordinary degree. With the relief of uremia, this picture of hyperconcentration supervened and was apparently responsible for the reappearance of coma and eventual death.

TABLE IV (CASE 4). INTAKE AND OUTPUT, BODY WEIGHT, AND CHEMICAL STUDIES

HOSPITAL DAYS:	1	2	3	4	5	6
Intake (c.c.)	2,000	2,000	2,700	1,000	2,200	3,400
Output urine (c.c.)	6,400		4,400	6,700	1,700	2,400
Chloride (meq./L)	104	115	120	123	127	128
CO_2 combining power (meq./L)	15	25	28		28	27
Sodium (meq./L)				153	171	172
Potassium (meq./L)		3.8	4.0	4.3	4.9	5.6
BUN (mg. %)	135	64	43	39	37	49
Creatinine (mg. %)			1.7			
Glucose (mg. %)	375	318	376			
Urine						
Specific gravity	1.011					
Glucose	1+					
Sediment	Occ. R.B.C.					
Body weight (kg.)	97.6	92	91	91		

CASE 5 (U. H. No. 725414).—D. D., an 81-year-old woman, underwent a combined abdominoperineal proctosigmoidectomy for a low-lying carcinoma of the rectum. Preoperatively she was felt to be in good physical condition despite her age, and there was no evidence of pre-existing cardiac or renal disease. Preoperative preparation had included oral succinylsulfathiazole and streptomycin. The patient withstood the procedure and the immediate postoperative period except for a brief episode of shock occurring after her transfer to the recovery room. At this time the blood pressure fell from a normal systolic reading of 170 mm. Hg to 80, but responded satisfactorily to the administration of 500 c.c. of whole blood.

Five days after operation a partial separation of the wound developed which required resuture with steel wire. After the discontinuance of nasogastric suction, it was impossible for the patient to achieve adequate fluid intakes, so that large amounts of intravenous fluids were required. Later jejunal tube feedings were resorted to.

On the eighteenth day after operation, because of the finding of basal râles and some decrease in urine output with associated weight gain, digitalization was begun and 1 c.c. of Mercuhydrin was given. This resulted in a slight diuresis on the thirtieth postoperative day (Table V). Since the patient still refused to accept any adequate amount of oral fluids, intravenous therapy had to be continued with supplementation at various times with jejunal feedings of glucose solution and milk.

On about the thirty-second postoperative day, the patient's condition started to deteriorate rapidly. She became stuporous, comatose, and finally unresponsive. It was at this time that the chemical evidence of hyperconcentration was first observed. She became rapidly worse. On the thirty-seventh day after operation, the temperature rose to 104° F. and the patient died.

An autopsy showed partial atelectasis involving both lungs with superimposed bronchopneumonia. There was a small area of necrosis of the descending colon with local abscess formation but no peritonitis. An organizing thrombus was present in the left iliac vein. Examination of the kidney revealed only intimal and elastic thickening of the small arteries and a few hyalinized glomeruli. There was slight dilation of the proximal convoluted tubules and vacuolation of the tubular epithelium which was not severe and could have represented post-mortem change.

Blood, Chemical, and Laboratory Findings.—Table V shows the intake and output data and laboratory findings on sample days after the surgical procedure. The chloride levels were depressed during the early part of this period and the urea nitrogen concentrations were not particularly elevated. The first evidence of hyperconcentration occurred on about the thirtieth day with chlorides rising to 110 and subsequently to 127 and 142 meq. per liter. This was associated with a rising blood urea nitrogen and acidosis as signified by the falling alkali reserve. This occurred despite the daily administration of over 3,000 c.c. of fluid. The chemical manifestations of gradually deepening coma coincided with these chemical developments.

TABLE V (CASE 5). INTAKE AND OUTPUT, BODY WEIGHT, AND CHEMICAL STUDIES

POSTOPERATIVE DAYS:	3	18	30	33	34	35	36	37	PRE-OP.
Intake (c.c.)									
oral and IV	3,065	2,950	2,750	3,650	3,450	3,300	3,500	4,000	
NaCl (Gm.)	8.6	4.5		4.5	9				
Blood (c.c.)	500		250 plasma		500				
Output urine (c.c.)	2,150	1,500	2,300	950	375	450	210	375	
Hemoglobin (Gm. %)	11.5		13.3		14.6	13.7			14.1
Chloride (meq./L)	88	77	110	127	142	122	121	118	113
CO_2 combining power (meq./L)	28	24	24	17	13	13	8	12	26
Sodium (meq./L)						178		154	
Potassium (meq./L)						4.7		4.5	
BUN (mg. %)		23		119	145	165	180	188	19
Creatinine (mg. %)				2.3	3.5	4.1		4.7	
Protein (Gm. %)					6.7	6.7			6.9
Urine									
Specific gravity	1.010				1.012		1.008	1.012	
Glucose	2+				1+		1+		
Albumin	Trace				1+		1+		
Urine chloride (meq./L)							15.5	8.6	
Sediment	Occ. casts				Occ. W.B.C.		Occ. W.B.C.		
Body weight (kg.)	53.9	58.4	54.6	48.8	47.5	49.2	49.6	51	

DISCUSSION

Fig. 1 shows the electrolyte patterns of the five cases which have been discussed along with the normal values of Gamble.[6] This representation illustrates the extreme increases in total ionic composition of the plasma which occurred, particularly in Cases 2 and 3, in which the total base values apparently exceeded 200 meq. per liter.

Although it is unlikely that any single common factor can be implicated as the basis for the occurrence of the electrolyte anomaly in the five cases, there are several clinical aspects which they all shared. It is apparent that the patients were not dehydrated in the usual sense. Reasonable fluid intakes and urine output quantities were present in all except Case 3 wherein a short period of inadequate water intake preceded the development of severe symptoms. In all instances the specific gravity of the urine was low, indicating some sort of failure in the renal response to the hyperconcentration of the plasma.

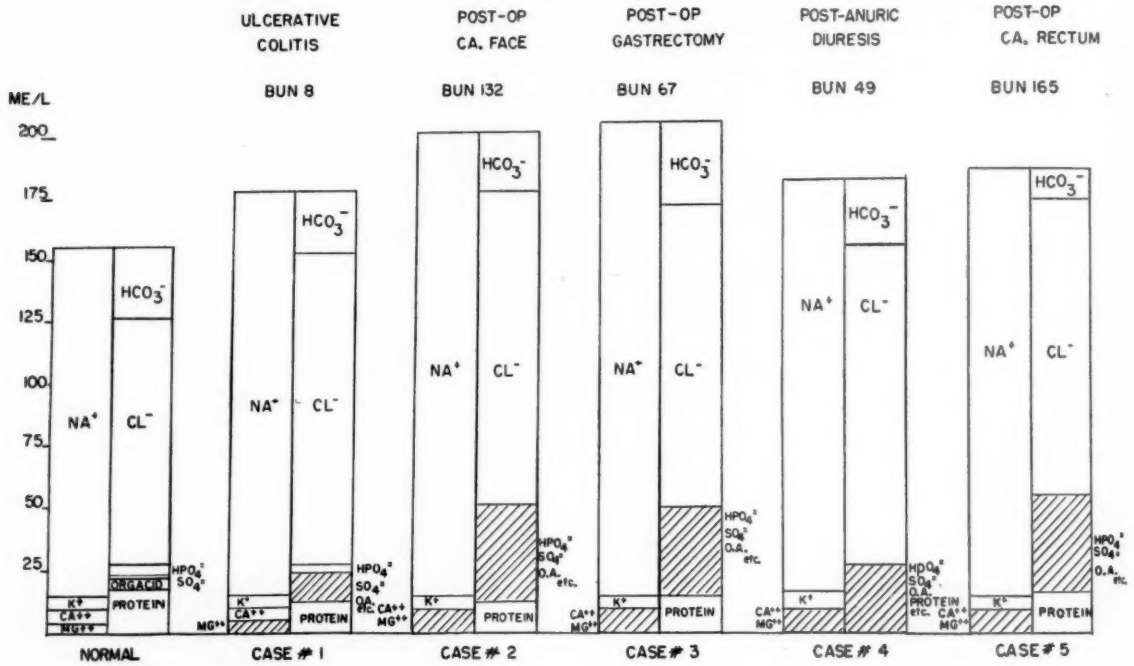

Fig. 1.—Serum electrolyte values in normal individual (after Gamble) and in the five patients at the height of electrolyte distortion. Cross-hatched areas indicate quantities which were not determined, but which were calculated by subtraction from the total base (anionic column) or in which normal values were substituted (cationic column).

High fever was characteristic of the course of all these patients and its onset clearly coincided in time with the appearance of the distorted electrolyte pattern. Profound central nervous system depression was also common to all the cases. The neurological manifestations were of particular interest in Patients 2 and 3, both of whom exhibited muscular twitchings and grasping and athetoid movements which were suggestive of basal gangliar disturbance.

At least four mechanisms have been proposed as agents in the pathogenesis of disorders of this type and deserve to be considered with reference to these cases. These mechanisms include toxic renal damage, brain injury, endocrine factors, and circulatory factors.

Renal Damage.—Luetscher and Blackman, in 1943, reported high sodium and chloride levels and permanent brain damage in patients who had suffered kidney injury from sulfathiazole.[1] A somewhat similar situation was reported by Maisel and co-workers[7] and a case with findings similar to those described

by Luetscher[1] following sulfadiazine administration was reported by Goodale and Kinney.[2] In these cases the secretion of a dilute urine with selective retention of sodium and chloride was demonstrated. In the cases reported here, sulfonamides were not used (except for preoperative use of succinylsulfathiazole in Patient 5). A host of antibiotic agents were, of course, employed, and although renal damage of this type could conceivably result from these agents, there is no direct evidence from our cases nor suggestion from the literature that such an action can occur. In those of our cases which came to autopsy, varying degrees of renal damage were found. Tubular damage of the type seen in the lower nephron syndrome was in evidence, though these changes were not extensive in any of the cases. Of particular interest was the one case (Case 2), coming to autopsy five months after recovery from the electrolyte disturbance, in which evidence of tubular regeneration was still present.

In the fifth patient, who died following abdominoperineal excision of the rectum, it was suggested that the use of Mercuhydrin might have been the mechanism for renal damage which resulted in sodium and chloride retention. This would seem an unlikely explanation in view of the fact that chloruresis is agreed to be a fundamental part of mercurial diuresis. It is true that inhibition of salt excretion has been reported with toxic doses of mercurials in animals,[8] but there is no evidence that this occurs with ordinary dosages. The possibility that the mercurial compound could contribute to the functional impairment of an already damaged kidney, does, of course, exist.

Postanuric Diuresis.—Severe retention of sodium and chloride with hyperconcentration of these ions in the plasma has been reported during the diuresis which follows a period of anuria in association with the lower nephron syndrome.[9] This is by no means the usual situation which obtains during the recovery from anuria of this sort. Much more frequently, difficulty is encountered consequent to the profound loss of salt which occurs during this phase when tubular reabsorptive capacity has not recovered and a urine closely resembling glomerular filtrate is excreted. Nevertheless, in occasional cases, salt retention occurs. A course of events closely resembling this seems to have occurred in Patient 4, who apparently suffered renal damage secondary to lower urinary obstruction. Profuse diuresis resulted in rapid fall in blood urea, but retention of electrolytes and their concentration in the plasma. Following an initially satisfactory clinical response the patient reverted to coma and apparently succumbed to the hyperconcentration. It appears likely that had the situation been recognized and very large quantities of salt-free fluid given, his life could have been saved.

Central Nervous System Lesions.—Hypernatremia and hyperchloremia, with pathologic retention of these salts by the kidney, have been reported in association with lesions of the brain. In general, this syndrome has been observed with two types of lesions: those involving the frontal lobes and those involving certain areas of the hypothalamus. Allot described sodium and chloride retention without ostensible renal disease in five patients, four of whom had brain lesions.[3] Sweet and co-workers studied in detail the hypernatremia and

hyperchloremia in a patient with a frontal lobe lesion. This patient, incidentally, also received sulfathiazole for urinary infection.[4] McCarty and Cooper have discussed this problem recently in connection with a case in which surgical ligation of the anterior cerebral arteries produced the syndrome of hypernatremia, hyperchloremia, and hypochloruria.[5] Experimentally, unilateral lesions of the hypothalamus have been shown to cause chloride retention.[10]

It is a perplexing fact that, although elevated electrolyte concentrations can cause brain damage as in the cases of Luetscher, a converse relationship also exists; namely, that brain damage can cause elevation of the electrolyte levels. In the first case reported here the question arose as to whether the intracranial hemorrhage could have been responsible for the electrolyte changes which occurred. Against this suggestion is the observation of rising electrolyte values several days before the acute episode which presumably was caused by the hemorrhage. On the other hand, one cannot be sure that some degree of damage had not taken place before the massive bleeding occurred.

Endocrine Factors.—The possible relationship of endocrine secretion to the development of this picture has been discussed.[4] It is likely that adrenal hormones with salt-retaining activity are produced during stress and are therefore active during the postoperative period and in relationship to serious illnesses. In hyperadrenalism of the Cushing syndrome type, slight elevation of the sodium and total base is frequently seen.[11] Ordinarily, adrenal hormones do not produce strongly elevated sodium and chloride levels. Though prolonged administration of substances like desoxycorticosterone in animals does produce increased water turnover and a diabetes-insipidus-like picture, this situation is not characterized by extraordinarily high electrolyte levels.[12, 13] The operation of adrenal hormones in this condition cannot perhaps be finally excluded, however, since the situation may be different in experimental animals which are able to drink ad libitum to satisfy their thirst and patients who are receiving the majority of their fluids by parenteral routes.

Browne, Karady, and Selye have shown that during the reaction to nonspecific stress in animals, a period of hyperchloremia occurs during the resistance phase, following the hypochloremia of the shock phase of the adaptation syndrome.[14] This rise is presumed to be the result of adrenal hyperactivity.

We have observed a similar course of chloride and sodium levels following operations in man but only rarely have found that the rise in chlorides actually exceeds the normal or preoperative level.[15] When hyperchloremia does occur it is slight and of short duration.

It should be pointed out that the electrolyte pattern under discussion does not resemble that of diabetes insipidus in which the sodium level, when it has been observed to be elevated, has been only slightly so.[16, 17] Nor does the pattern resemble that of anorexia nervosa (a clinically reasonable diagnosis in Case 3) in which, as in voluntary starvation, blood sodium and chloride levels have been shown to be depressed.[18]

Circulatory Factors.—Borst has described severe hypernatremia and hyperchloremia in instances of massive gastrointestinal hemorrhage.[19] This finding

led that author to further investigations from which he postulated that renal retention of sodium occurs as a response to decreased cardiac output and that this process is, in fact, an important mechanism for the preservation of cardiac output.[20] This hypothesis is of course closely related to the so-called "forward failure" theory for the causation of edema in cardiac decompensation. Severe hemorrhage was not a factor in any of the cases mentioned above. However, the mechanism described by Borst merits further investigation, and estimations of cardiac output and blood volume would be of great interest in patients with these findings. The short period of shock which followed the operation in Case 5 no doubt contributed to renal impairment.

CONCLUSIONS

It is not profitable to speculate further on the basis of present knowledge as to the chain of events which resulted in hypernatremia and hyperchloremia in these patients. It is apparent that renal impairment, either functional or anatomic, was the immediate cause of the electrolyte distortion. The situation can develop in the presence or absence of uremia. It does not seem unreasonable that any mechanism of renal injury, whether toxic, infectious, or circulatory could result in this type of functional disturbance. In addition to these, deviations of the normal humoral and nervous regulators of renal function must be considered and require further investigation.

It appears that the hyperconcentration of electrolytes is, by itself, a grave situation. The condition should be suspected in the presence of sudden high fever and central nervous system depression. Clearly, the serum sodium determination is of the greatest value in the recognition of this state, since, in the presence of uremia, the measurable anionic components may be reduced by the presence of abnormally retained acid radicals. Although our clinical experience is inadequate, there is good reason for the belief that prompt recognition of the anomaly and the administration of very large amounts of fluid without salt should be able to reverse the symptoms of hyperconcentrated electrolytes. This apparently was accomplished in the one individual who survived.

SUMMARY

1. Five cases have been presented in which severe hyperconcentration of electrolytes occurred in the absence of water deprivation and with relatively normal outputs of urine with low specific gravity.

2. This picture is characterized clinically by pyrexia, severe central nervous system depression, and in some instances by abnormal neuromuscular activity.

3 The most reliable chemical index of this situation is elevation of the serum sodium level. Chloride is also elevated and azotemia may or may not be present.

4. The possible renal, neural, endocrine, and hemodynamic factors underlying the development of severe hypernatremia are discussed.

We are indebted to Dr. Norman H. Jacob of the University of Minnesota Department of Pathology for reviewing the kidney sections of these patients.

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CAROTID BODY TUMORS

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CAROTID body tumors are not frequently encountered, but due to the seriousness of these neoplasms and the importance of administering adequate treatment to eradicate them, eight cases are reported. Early diagnosis, recognition of the extent to which such tumors may develop, and prompt and adequate surgical care are essential in the management of these tumors. Their unusual location, in the carotid triangle, readily permits them to wind around and envelop the common, internal, and external carotid arteries,[25] the jugular vein, the vagus, hypoglossal, and glossopharyngeal nerves, and the sympathetic chain of nerves, and to encroach upon the pharynx. In addition, if permitted to persist, a substantial percentage[21] undergo malignant change. Carotid body tumors must be differentiated from other tumors located in the same area whose growth is slow and persistent and which may also undergo malignant transformation.

The operative removal of carotid body tumors may be very perplexing and formidable even to the most adept neck surgeon. If permitted to persist and extend their growth, at times to the base of the skull, the technical difficulties encountered in their removal, especially when there is evidence of malignant change, frequently result in considerable residual disability and in appreciable morbidity and mortality rates.

ANATOMY AND HISTOLOGY

Anatomy of the Carotid Body.—The carotid bodies occur bilaterally and are situated in or near the crotch of the common carotid artery.[1, 30] Due to the occasionally varying location of the bifurcation of the common carotid artery, there may be variability in the clinical location of the tumor. It is known that the bifurcation of the common carotid artery may be above or below the standard level.[17] It occurs higher than usual in most abnormal cases, even up to the base of the skull; less frequently, it may be as low as the root of the neck. On very rare occasions the common carotid artery may ascend in the neck without any subdivisions. Carotid body tumors developing in the presence of such an anomaly would be found from the base of the neck to within the intracranial cavity. In one of this group of eight cases, the common carotid artery bifurcated at the level of the cricoid cartilage, and in another the bifurcation occurred almost at the base of the skull[17]; consequently, the location of the tumor in the former was low in the neck (Fig. 1), and in the latter, very high in the neck.

The average carotid body is about 4 by 6 by 2 mm. in size[42] and brown, reddish brown, gray, or a mixture of these, in color. It is ovoid in shape and surrounded by a fibrous capsule which sends septa into the parenchyma of the gland, dividing it into multiple lobules. The vascular and nerve supplies penetrate these septa to enter the gland which is rather firmly fixed in the crotch of

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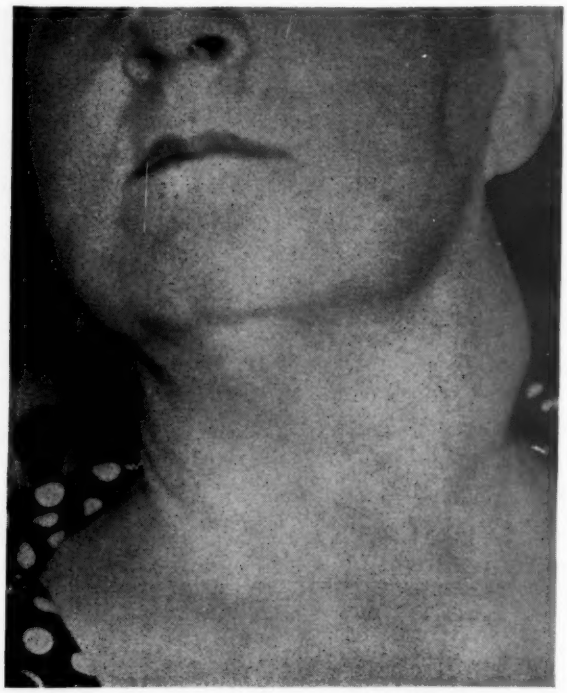
the carotid artery by fibrous connective tissue. The blood supply of the gland is derived from small twigs from the external and internal carotid arteries. The nerve supply is from the sympathetic ganglion, the glossopharyngeal, vagus, and hypoglossal nerves. It has been reported that there is atrophy of carotid bodies in elderly patients; however, in numerous cadaver dissections, macroscopically,



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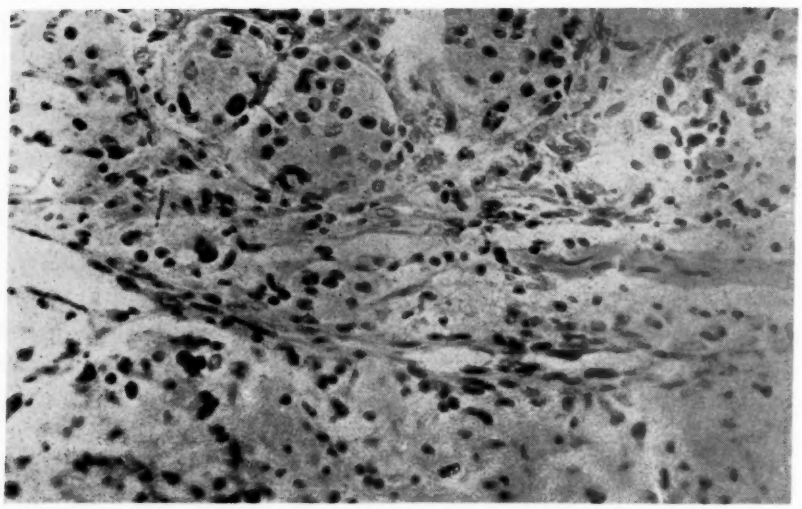


B.

Fig. 1.—*A*, Carotid body tumor, left side of neck, present nine years. This tumor was located in crotch of common carotid artery which bifurcated at level of cricoid cartilage, a rather unusual location for this type of tumor. *B*, Photomicrograph of tumor showing acini with large capillary sinuses throughout.

the carotid bodies appeared about the same size in all examined over the age of 15 or 16 years. Aberrant carotid bodies are reported to occur in unusual locations,[5] i.e., any place where sympathochromaffin tissue is located,[8, 10] such as the middle ear, mastoid process, and pancreas, and Zuckerkandl's bodies of the abdomen. It is thought by some that the glomus jugularis as reported by Gild[19] may be the origin of carotid body tumors.

Histology of the Carotid Body.—Histology of the carotid body shows the parenchyma to be composed of rather large polyhedral or cuboidal cells with pale-staining cytoplasm, which occur in strands or sheets, or form alveoli.[20] The cytoplasm is finely granular, and in fresh specimens the granules are chromopositive. The hyperchromatic nuclei are small and centrally placed. There is a rich network of nerves and vessels throughout the fibrosepta. Ganglion cells and some of the cellular elements exhibit an affinity for chromatic salts.

Physiologically, there is no evidence to substantiate any relationship between the carotid bodies and the glands of internal secretion. Although there is evidence of the presence of chromaffin granules which are thought to secrete adrenalin or an adrenalin precursor,[39] this has not been confirmed. It has been thought by some that the carotid body is associated with the carotid sinus and would act as a sensory organ containing chemoreceptors[22] which would respond to certain chemical changes in oxygen tension of the blood. It has been shown, however, that there is no relationship between the carotid body and the carotid sinus mechanism utilized in controlling blood pressure and chemical changes in the blood. The fact that carotid body tumors,[4, 6] either bilateral[27] or unilateral, do not produce symptoms comparable to an abnormal function of the carotid sinus[42] such as convulsions, fainting, or dizziness, and the fact that there is no apparent physiologic change in the patient following removal of these tumors, are substantial evidence that there is no relation between carotid bodies and the carotid sinus.

HISTORY

Von Haller, in 1743,[20] mentioned the carotid body and referred to it as the *ganglion minutum*. About 1862, Luschka[28] made a careful and detailed microscopic study of the carotid body, and referred to it as the *ganglion intercaroticum*. Luschka was of the opinion that carotid bodies are part of the sympathetic chain and intimately related to the anterior lobe of the hypophysis.

Marchand, in 1891,[30] reported the surgical removal of a carotid body tumor which necessitated ligation of the common carotid artery and the jugular vein, as well as removal of the sympathetic, vagus, and hypoglossal nerves. His patient died on the third postoperative day. Madyl and Gersuny[25, 28] each reported the removal of a carotid body tumor with recovery of his patient. The common, external, and internal carotid arteries were ligated in each case; Madyl's patient developed hemiplegia and facial paralysis, but recovered after a period of time. Scudder[40] reported successful removal of a carotid body tumor with verified histologic study of the tumor, and brought the literature up to date. Since that time there have been reports throughout the medical litera-

ture from individual surgeons or clinics, and numerous case reports and reviews of the literature have appeared; some authors have reported bilateral locations of the tumors.[21, 25, 27, 32, 34, 43]

PATHOLOGY

The only pathologic lesion or disease of the carotid body yet observed and reported is tumor formation. Grossly, these tumors,[26] reddish brown in color, remain to a large degree ovoid or spheroid, lobulated, and encapsulated, unless malignant transformation takes place. Their size may vary from 1 or 2 cm. to 10 cm. in diameter, and in accordance, they may weigh a few grams or many; Reid[35] reported one weighing in excess of 190 Gm. These tumors are firmly attached in the crotch of the carotid artery; their growth is slow, and as they enlarge they eventually encircle the carotid vessels but remain firm and compressible until malignant transformation occurs, after which they develop the typical hardness of malignancy. Carotid body tumors have been classified by various authors as endotheliomas,[15] paragangliomas, neuroblastomas, adenomas, peritheliomas, and simple carotid body tumors.

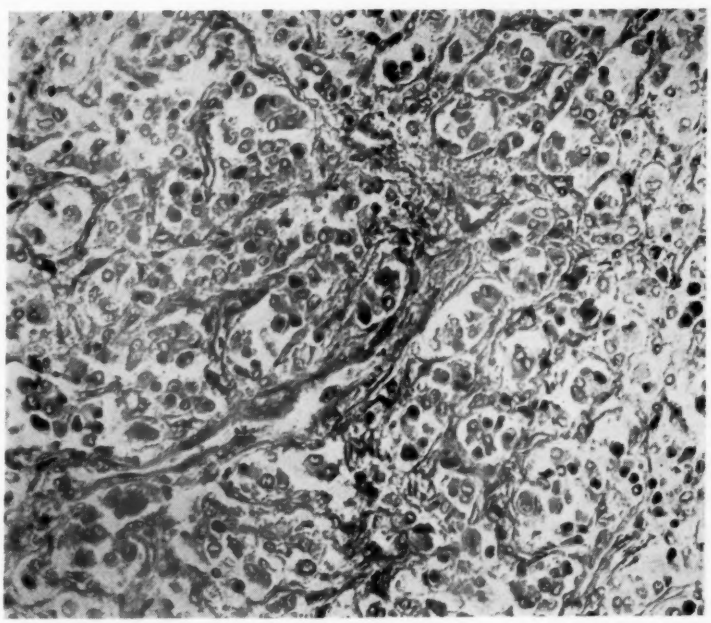
Histologically, carotid body tumors are formed, in most instances, by proliferation and hyperplasia of the cells normally observed in the carotid body, and since there is no evidence of adenoma formation, are considered by some to be only excessive proliferation of normal cells except in cases where malignant change takes place. Harrington, Clagett, and Dockerty,[21, 43] observed two rather characteristic histologic patterns, alone or mixed, in their series. They designated one pattern as *insular* or *alveolar* (Fig. 2), the other as *peritheliomatous,* with the latter predominating. The alveolar pattern is illustrated by large islands of polyhedral cells that are separated by narrow bands of connective tissue without much hyalinization. The fibrous tissue is permeated by thin vascular sinuses lined by endothelial cells that insinuate themselves between the alveolar cells and the blood vessel walls. Old blood pigment frequenty is distributed throughout the stroma in this group, and parenchymatous tissue occupies a large part of the microscopic field. The second pattern, termed peritheliomatous, is composed of smaller cellular units which tend to form alveolar structures. There also appear small groups or clumps of cells arranged in nests, sheets, or strands and separated by vascular sinuses in the connective tissue stroma. Blood sinuses are abundant. Hyalinization of the fibrous connective tissue in some areas might suggest that tumors in this group resemble the mixed tumors of salivary origin.

Carotid body tumors undergo malignant change, evidenced by cellular variation, active mitosis of the cells, and invasion of the capsule and adjacent structures, in from 40 to 50 per cent of cases as reported by Harrington, Clagett, and Dockerty.[21] It was the opinion of these authors, based on histologic study, that these tumors should be regarded as low-grade malignancies with potential powers of invasion and metastasis.

LeCompte and co-workers, in an analysis of seventeen cases,[26] found no evidence of malignant transformation in microscopic studies. They did observe

variation in nuclear size, but pointed out that similar nuclear changes are observed in other benign tumors. Lahey and Warren[25] in a series of twenty-two carotid body tumors, found no conclusive evidence of malignant change; one case was considered locally malignant although there were no definite metastases to the cervical lymph nodes.

A.



B.

Fig. 2.—*A*, Carotid body tumor, left side of neck, present twelve years. Patient had been treated elsewhere one year previously with irradiation therapy with no subsidence of symptoms or decrease in size of tumor. *B*, Photomicrograph showing alveolar pattern type of tumor.

Two cases in the present group showed microscopic evidence of malignant change, and in each instance there was infiltration of the surrounding tissue. In one case the capsule was penetrated, and the tumor had invaded the sternomastoid muscle; a radical neck dissection was carried out in this case and none of the forty-four lymph nodes removed were found to be involved by the tumor. In another case, in which the tumor had been present for a period of six years and had shown rapid growth and fixation in the six months previous to admission, there was definite infiltration of the sternomastoid muscle and microscopic evidence of malignancy at operation. Both of these patients were alive and well over five years after radical removal of their tumors. None of the other six cases in this series showed local invasion of adjacent structures or microscopic evidence of malignancy.

Lahey is of the opinion that the tumors reported in a series of cases from the Lahey Clinic which have undergone malignant transformation should be classified as *glomus jugularis*,[19, 45] and since they occur in the same anatomical proximity, they may be confused with carotid body tumors.

CLINICAL BEHAVIOR

Carotid body tumors are located deep beneath the sternomastoid muscle in the crotch of the carotid triangle and are unilateral, or occasionally bilateral. Their growth is slow, persistent, and essentially asymptomatic. Some of the complaints of the patients in this series were pain in the face and neck, hoarseness, and occasionally, dysphasia. Thrill and bruit, when observed, are due, in all probability, to the proximity of the tumor to the carotid vessels. In one case in this series, the recurrent laryngeal nerve was involved by the tumor; in another, the tumor had enlarged to produce pressure on the pharynx sufficient to interfere with swallowing. In two cases there were abnormal bifurcations of the common carotid artery as mentioned previously. In one instance the tumor was located at the level of the cricoid cartilage, and in the second it was high under the angle of the mandible.

When small, these tumors are movable in the horizontal plane but seldom in the vertical. They are compressible but firm, and may exhibit a bruit.[31, 33, 34] The larger tumors, due to pressure from surrounding structures, project to the base of the skull and inward to the pharynx, producing difficulty in swallowing. Two excessively large tumors in this group produced stretching of the hypoglossal nerve. Even very large tumors, due to their slow and gradual growth which frequently causes expansion of the surrounding tissues to a marked degree, may not produce many symptoms. In this series, the average length of time a tumor was present before consultation for surgery was eight years. In two cases bilateral tumors were present. Each of these patients gave a history of having had a tumor on one side for a period of two or three years before the opposite side became affected; in one of these a single tumor had violated the capsule and infiltrated the sternomastoid muscle.

These tumors do not move with deglutition. When small they are smooth, but larger ones may be nodular. In most instances they are located at the ap-

proximate level of the hyoid bone. Occasionally, carotid body tumors may be confused with aneurysms of the carotid artery, due to the expansion-like pulsation and thrill;[36, 43] however, pressure over the common carotid artery below an aneurysm will abolish the pulsation and thrill.

In this series, one patient with a very large tumor had a Horner's syndrome. There was unilateral enophthalmos, ptosis of the upper eyelid, constriction of the pupil on the involved side and absence of sweating on that side of the head, produced by involvement of the sympathetic chain and ganglia. Two patients complained of pain in the region of the middle ear, and several noted a condition referable to pressure on the cervical and occipital nerves.

DIAGNOSIS

Differential Diagnosis.—Any slow-growing tumor, essentially symptomless, ovoid in shape, and located deep in the upper anterior cervical triangle, should be suspected to be of carotid body origin. To be differentiated from tumors of the carotid body are branchiogenic cysts[15] and carcinomas, neurofibromas, metastases from carcinoma of the homologous lobe of the thyroid gland or from lesions above or below the clavicle, and tuberculous lymphadenitis. Metastatic tumors are stony hard, irregular, nodular, frequently multiple, and have histories of rapid growth.

Branchiogenic cysts, which usually arise in childhood, may be differentiated from carotid body tumors by their superficial location. Primary branchiogenic carcinomas may be distinguished from carotid body tumors in that they occur in an older age group, are immobile, and are not associated with pulsations[8] or bruits. Primary lymphomas may appear first as discrete nodes, located superficially or deeply in the cervical region; however, they have histories of rapid growth, and sooner or later appear elsewhere in the body.

Neurofibromas may occur anywhere in the body, especially in the neck. They have origin from nerve tissue, are usually located more laterally than carotid body tumors, are deep seated, and have few characteristics in common with carotid body tumors.

Diagnosis.—Any slow-growing, painless tumor located deep in the upper anterior cervical triangle, varying in size from that of a hazelnut to that of a large orange, should be assumed to be a carotid body tumor until proved otherwise[29, 31, 33] (Fig. 3). Carotid body tumors may occur at any age[31, 33]; the youngest patient in this series was 26 years of age, the oldest 60 years; there is no sex differentiation.

Laboratory procedures and roentgenologic examinations are of little value in establishing a diagnosis of carotid body tumor. Aspiration biopsy has been suggested, but is not recommended in deep-seated neoplasms occurring in the vicinity of the great vessels and nerves of the neck, because of danger of injury and hemorrhage.

TREATMENT

Essential in the ideal treatment for carotid body tumor is early, accurate diagnosis, while the tumor is still small and has not grown to surround and

involve the carotid vessels, permitting its removal without injury to, or ligation of, the common or internal carotid artery, or both. When larger tumors are encountered or malignancy is present, the patient and his family must be informed of the possible danger of operation. The patient should be advised that if the tumor is found to be malignant it may be necessary to sacrifice the common or internal carotid vessel, or both,[24, 27] which could result in hemiplegia or even death. It has been my practice to prepare patients who have a probable carotid body tumor or aneurysm of the carotid artery, and who may require ligation of the common or internal carotid artery, or both, by applying systematic, periodic pressure to the common carotid artery to improve the collateral circulation to the brain. This is best accomplished by compressing the common carotid artery with the thumb against the transverse process of the sixth cervical vertebra (Matas method) or with the Richard Light pressure apparatus.[42] The compression should begin with two or three minutes, three or four times daily, and continue for three or four weeks, increasing gradually, until the common carotid artery can be compressed for ten minutes, four or five times daily without central disturbances on one side of the body, fainting, or dizziness. Complete compression of the vessel has been accomplished when the temporal pulse is absent, and thrill and bruit, if present, are no longer observed.

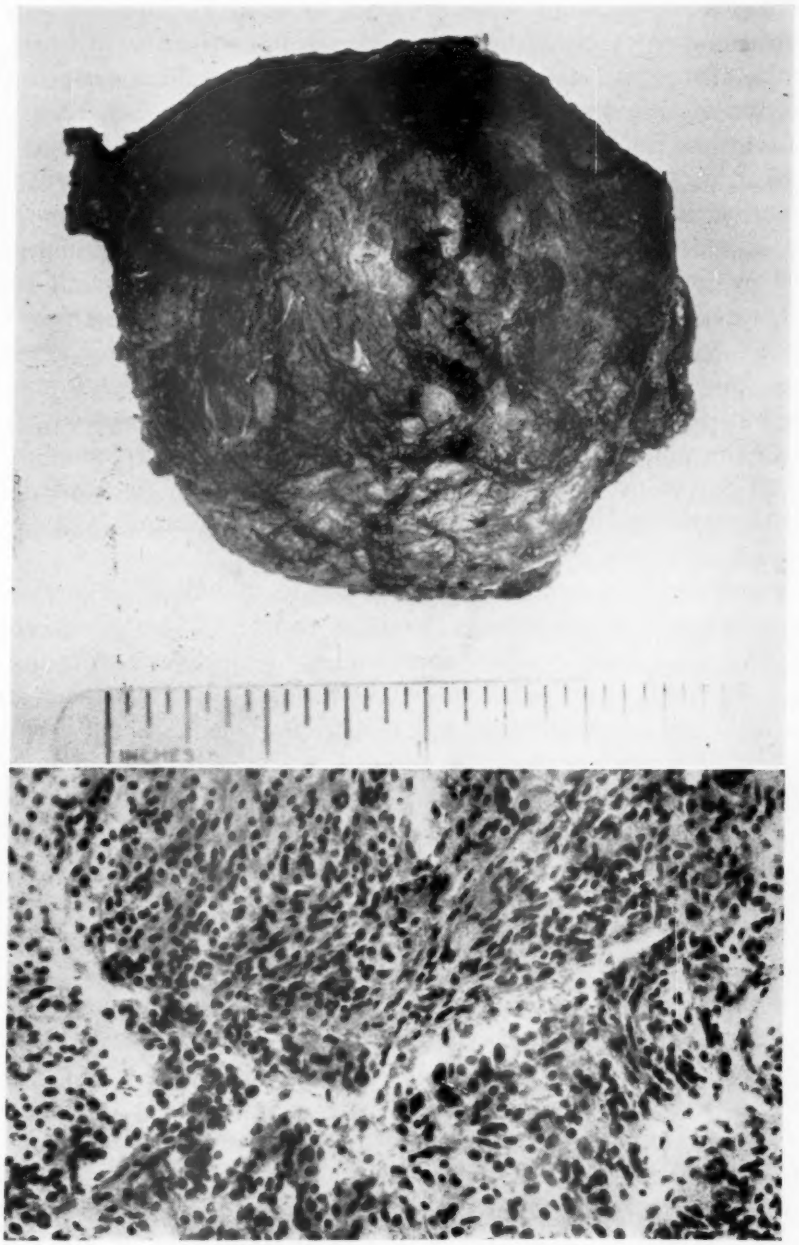
Fig. 3, *A*.—Carotid body tumor present six years, showing rapid growth for past year necessitating removal of external carotid artery. Tumor had enlarged to produce pressure on pharynx causing difficulty in swallowing.

Compression of the vessel for a period of ten minutes, four or five times daily for several weeks does not always insure the patient against the development of a cerebral vascular accident when it is necessary to ligate the common or internal carotid vessel. Lahey and Warren[25, 27, 42] reported a series of eighteen cases in which two patients withstood preoperative compression of the carotid vessels without any symptoms, but hemiplegia developed and the patients died following ligation of the carotid vessels during excision of their tumors. In another of their cases, hemiplegia and death followed excision of the tumor which

was dissected free from the carotid vessels; the hemiplegia was caused by a sclerotic plaque displaced from the intima of the vessels during manipulation of the tumor, producing a fatal carotid thrombosis.

There are others[32] who feel that systematic preoperative use of digital compression to promote collateral circulation to the brain is not effective if the

B.



C.

Fig. 3, *B* and *C*.—*B*, Photograph of tumor, showing external carotid artery embedded in tumor. *C*, Photomicrograph showing nests of polyhedral and cuboidal cells with some attempt to form alveoli. Numerous capillary sinuses are present. This represents the peritheliomatous pattern of carotid body tumors.

bifurcation has been removed; however, when the common carotid is ligated, collateral circulation may develop between the external carotid and subclavian arteries.

It was previously thought that age was a factor in considering mortality following ligation of the common or internal carotid artery. Dandy,[11] as well as Roberts,[36] and Pemberton and Livermore,[32] made the point that youth was no insurance against such complications. Reid[55] was of the opinion that elderly patients withstood carotid ligation better than younger ones.

Recently, Pemberton and Livermore[32] discussed cerebral complications following ligation of the common or internal carotid vessel and divided these into immediate and late complications. They gave three causes which may act alone or in combination to produce the immediate symptoms: (1) disturbance of the flow of blood to the brain, with sudden decrease of the oxygen supply to the brain, (2) stimulation of the carotid sinus reflex, and (3) stimulation of the periarterial sympathetics. However, these authors mentioned that stimulation of the sympathetics produces much less vasospasm of the cerebral vessels than of vessels elsewhere in the body. They also mentioned that earlier effects can be detected by the anesthetists during the surgical procedure and may be only transitory, but if the effects continue the ligature should be removed. On several occasions I have placed rubber-shod bulldog clamps over the common, external, and internal carotid vessels for periods of ten to fifteen minutes during the removal of carotid body tumors or aneurysms of the carotid artery without deleterious effects to the patients.

Pemberton and Livermore are of the opinion that delayed cerebral complications have origin in a thrombus in the distal end of the ligated internal cartoid artery, in which the thrombus propagates itself upward, involving the branches of the circle of Willis or an embolus breaks off. In such cases, symptoms appear from several hours to several days after ligation of the internal carotid artery. They demonstrated the length of the internal carotid artery in an autopsy specimen and found the length from the bifurcation to the point where it joins to form the circle of Willis to be approximately 17 cm.; hence, it is perfectly possible that a thrombus may develop in this long segment of the artery after ligation. For this reason, when it is necessary to ligate the internal carotid artery, these authors suggested that it should be done as near the base of the skull as possible.

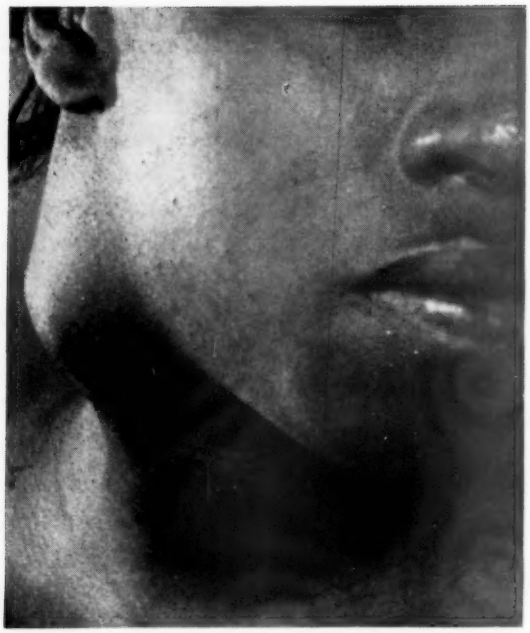
These same authors advocate the use of anticoagulants when it is necessary to ligate the internal or common carotid vessel, and state that their use has reduced the mortality. Following an earlier discussion and suggestions by MacComb,[29] Bigger,[3] and Pemberton and Livermore,[32] I have used anticoagulants in cases of aneurysm of the carotid artery, but have not had an opportunity to use them in cases involving the removal of a carotid body tumor. The method suggested by Pemberton and Livermore seems so feasible in the removal of carotid body tumors, as well as in aneurysms of the carotid artery, that this method which may be used prophylactically, is given here: 300 mg. Dicumarol are administered orally fifteen to twenty hours before operation when it seems likely that ligation of the common or internal carotid artery in aneurysms, or excision

of the bifurcation of the common or internal carotid artery in removal of carotid body tumors will be necessary. Heparin is started on the operating table if the vessels are sacrificed. This is given by continuous intravenous drip: 200 mg. heparin are added to 1,000 c.c. of 5 per cent dextrose in distilled water. Approximately 25 drops of this solution are given per minute, regulated in accordance with the coagulation time which is determined every eight hours for the first twenty-four hours and every twelve hours thereafter. The coagulation time is maintained between fifteen and twenty-five minutes. Oral administration of Dicumarol is resumed as soon after the surgical procedure as the patient is able to take the tablets. The dose depends on daily determinations of prothrombin time. When the prothrombin time has reached the desired level, the use of heparin may be discontinued, and Dicumarol alone given until the probable danger of a thrombosis is past. Pemberton and Livermore report that no complications or deaths occurred following the use of anticoagulants in four cases where either the common or internal carotid artery was ligated.

In a total of thirty-three carotid body tumor operations at the Mayo Clinic, ligation of the common and internal carotid arteries was performed fourteen times with five deaths, all preceded by hemiplegia. In two of these cases thrombosis of the middle cerebral artery was demonstrated at autopsy. These figures show ligation in 50 per cent of the patients operated upon, with death in 30 per cent of those in whom ligation was done.

It has been my policy for some years to infiltrate the adventitia of the common carotid artery with 1 per cent procaine solution, using a very fine needle, in all cases in which there is manipulation of the common carotid artery, or ligation of the external carotid artery when the vessels are first exposed in the operative procedure; this can be done without damage to the vessels. In addition, if a large carotid body tumor is present, the stellate ganglia and the first and second cervical ganglia are also injected with the procaine solution.

Surgical Treatment.—The surgical technique applied in the removal of a cartoid body tumor begins with a wide exposure of the carotid vessels and surrounding structures to permit accurate appraisal of the problems which may be encountered in removal of the tumor. An incision is made along the anterior border of the sternomastoid muscle from the calvicle to the mastoid process; the cervical fascia is opened and the sternomastoid muscle and internal jugular vein are retracted laterally; the omohyoid muscle is severed and retracted as it passes anteriorly across the jugular vein. The carotid artery and vagus nerve are exposed from the clavicle to well above the bifurcation of the artery. All tumors in this series were found in the crotch of the carotid artery; they may be medial or lateral to the bifurcation but are definitely always associated with the bifurcation (Fig. 4). If the tumor is small it may be dissected readily from the carotid vessels; if larger, it frequently is intimately attached to the adventitia of the vessels with very firm fibrous connective tissue. By placing a separate strip of umbilical tape around each of the common, internal, and external carotid arteries, these vessels can be retracted or the internal and external carotid arteries can be separated, permitting the tumor to be more readily dissected from the vessel walls. When the tumor seems to have completely invested the vessels,



A.

B.

Fig. 4, *A.*—Branchiogenic cyst, right side of neck, present nine years; note superficial location of cyst. *B,* Photomicrograph, cyst wall.

and appears very vascular, I have found it advantageous, in addition to using umbilical tape for retraction, to place a rubber-shod bulldog clamp around the common carotid artery and to ligate the internal jugular vein low in the neck and at the base of the skull. If necessary, smaller clamps may be placed high up on the internal and external carotid arteries, allowing the tumor to be dissected with less likelihood of hemorrhage (Fig. 5). These clamps have been left in place for periods of ten to fifteen minutes without injury or accident to the patient. If a longer period is required for the dissection, they are removed for a few moments then reapplied.

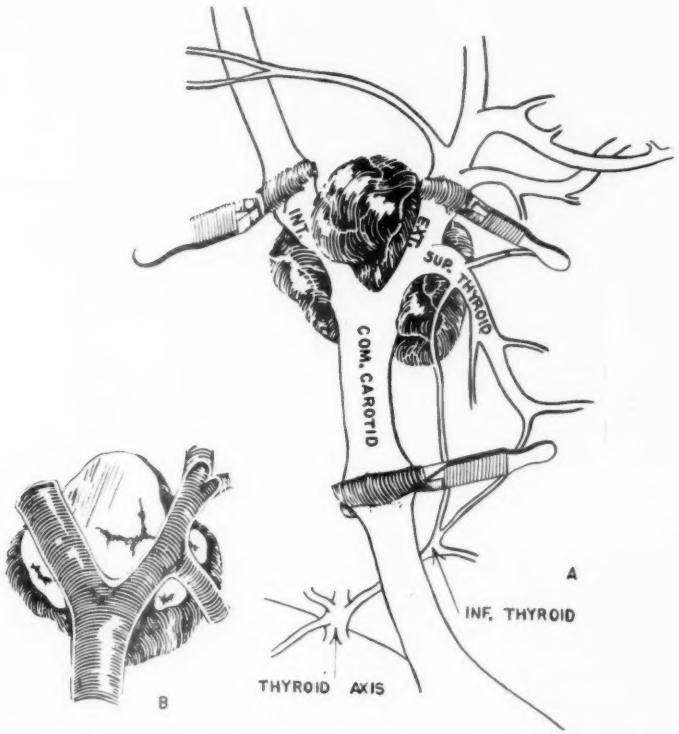
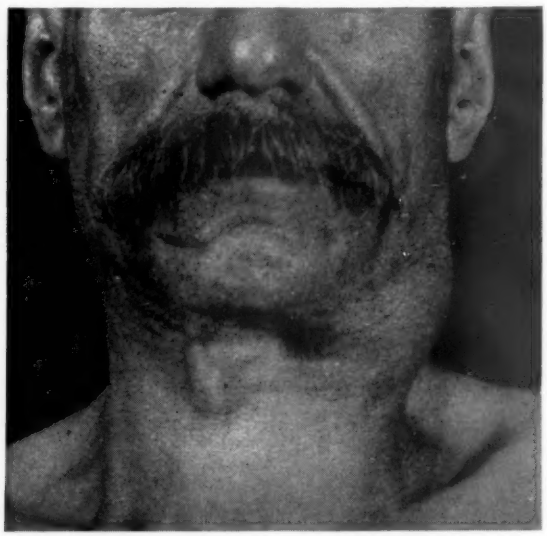


Fig. 5.—*A*, Carotid body tumor in crotch of common carotid artery. Rubber-shod bulldog clamp shown applied to common carotid artery and internal and external carotid branches which facilitates removal of tumor without injury to vessel walls and prevents troublesome bleeding. *B*, Cross-section of carotid vessels showing that tumor had not invaded vessel walls. (From Ward and Hendrick: Tumors of the Head and Neck, Williams & Wilkins Company.)

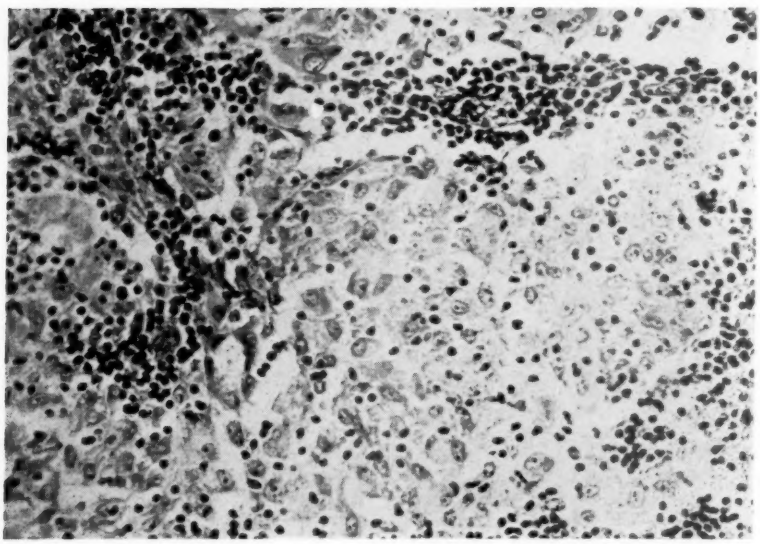
Tumors which at first may appear to be completely adhered to the vessels have been dissected out by developing a line of cleavage between the vessel walls and the tumor and severing the fibrous connective tissue with dissecting scissors. On three occasions in the removal of tumors in this series it was necessary to sacrifice the adventitia on one or both vessels, and in four instances the external carotid artery was ligated and removed with the tumor because it had been completely enveloped by the tumor. This vessel may be ligated without hesitancy and frequently is in radical neck dissections and resections of the mandible and floor of the mouth and tongue for various types of malignancy. In one case in this series in which the tumor had completely encircled the carotid vessels and invaded the sternomastoid muscle (Fig. 6), all the carotid vessels were ligated

and excised along with the internal jugular vein, hypoglossal nerve, and sternomastoid muscle because of malignant transformation of the tumor. This patient had hemiplegia for a period of several days and aphasia for several months. There was complete recovery, and seven years later there had been no recurrence.

Larger tumors which seem virtually "stuck" between the base of the skull, the lateral wall of the pharynx, and the crotch of the carotid artery may be dissected out of this position without too much difficulty by using umbilical tape



A.



B.

Fig. 6, *A*.—Malignant carotid tumor which had been present for sixteen years, developed rapid growth during few months preceding operation with pain in ear and difficulty in swallowing. Tumor had invaded capsule and infiltrated into sternomastoid muscle. Radical neck dissection performed with complete removal of tumor and preservation of common and internal carotid arteries. No recurrence seven years later. *B*, Photomicrograph showing tumor invading sternomastoid muscle.

to retract and separate the internal and external carotid arteries. In one case in this series a patient had, in addition to the tumor high in the cervical area of the left side of the neck, an adenoma of the thyroid gland. This was thought by his physician to be malignant, and the tumor in the cervical area to represent metastasis. The patient was operated upon elsewhere, and the adenoma was removed. Although the cervical tumor did not show malignant transformation, the patient was given irradiation therapy over the tumor, with no decrease in its size. Later the patient developed difficulty in swallowing and was referred for surgical excision of the high cervical tumor. At operation, the tumor was firmly attached to the base of the skull, and medially to the pharyngeal wall. By placing a rubber-shod bulldog clamp below the bifurcation[42] of the common carotid artery, producing retraction with umbilical tape on the internal and external carotid arteries, severing the digastric muscle and elevating the hypoglossal nerve and having an assistant place one finger deep in the patient's mouth with pressure over the lateral pharyngeal wall, the tumor was delivered without injury to the hypoglossal nerve, cervical sympathetic plexus, or carotid vessels.

In the removal of a large tumor which was adhered posteriorly to the cervical sympathetic ganglion and plexus, these structures were injured, and the patient developed a Horner's syndrome. Extreme care should be exercised in the operative procedure to prevent injury to the sympathetic chain which lies beneath the carotid vessels so as to prevent this condition, which is disabling to the patient. Since the hypoglossal nerve passes across the carotid vessels, jugular vein, and vagus nerve above the carotid crotch, it is important, in the removal of a carotid body tumor, to dissect the nerve out early in the surgical procedure to prevent its injury. If it seems likely that there will be injury to the nerve, it may be severed at the crossing of the vessels, and resutured upon completion of the operation; however, good results have not been obtained following this practice in surgical procedures carried out for other conditions in this area.

In bilateral carotid body tumors, it should be the policy to remove the one which has the appearance of being more advanced at the first operative procedure. This condition was encountered in a 45-year-old man who gave a history of having had a tumor in the right anterior cervical triangle for approximately ten years. About six years after the appearance of the first tumor, the patient observed a similar one in the same area of the opposite side of the neck. One year previous to admission, the first tumor developed rapid growth, causing pain in the ear and upper cervical area of the spine, and difficulty in swallowing. Examination revealed a tumor the size of a small orange, located deep in the right anterior cervical triangle and having the appearance of a carotid body tumor. In the left side of the neck there was a tumor comparable in size to an English walnut, movable horizontally but not vertically, located deep in the left anterior cervical triangle. Since the larger tumor was producing definite symptoms, it was elected to be removed first. At operation the sternomastoid muscle was found to be invaded by a tumor located in the crotch of the carotid artery. The internal jugular vein was ligated low, and the dissection was extended upward; a rubber-shod bulldog clamp was applied to the common carotid artery; the external carotid artery was ligated and the tumor mass was dissected free from the internal

carotid artery. Frozen section revealed that the tumor was malignant; therefore a radical neck dissection was performed, including removal of all structures from the clavicle below to the base of the skull above, with preservation of the internal and common carotid arteries and hypoglossal, vagus, spinal accessory, and phrenic nerves. None of the sixty lymph nodes removed were involved by the tumor. Three months later the tumor on the left side of the neck was exposed and readily removed from the crotch of the carotid artery. It was not necessary, in this instance, to ligate the internal jugular vein or the external carotid artery. This tumor was benign and the patient has remained well with no recurrence when last contacted five years later.

Ward and Hendrick[43] have shown that it is feasible to carry out bilateral radical neck dissections with removal of both internal jugular veins and ligation of both external carotid arteries with no appreciable edema developing in the face, nor vascular disturbance of the tissues supplied by the external carotid arteries, if the dissections are spaced from six to twelve weeks apart. In two instances these authors found it necessary to perform simultaneously bilateral ligations of the external carotid arteries, due to excessive hemorrhage in cases of juvenile nasopharyngeal fibroma. There was resultant necrosis of the tip of the tongue in both cases.

Roentgen Therapy.—This modality of treatment for carotid body tumors was suggested in 1929, by Bevan and McCarthy,[2] who reported good results with its use. Since that time, roentgen therapy has been utilized with enthusiasm by some and has been administered to very large tumors which were considered inoperable. However, Phelps, Case, and Snyder[33] reported seven proved cases of carotid body tumors treated with irradiation therapy (x-ray and radium) without any appreciable benefit. Lahey and Warren[25] reported three cases in their group treated with irradiation therapy with only slight reduction in the size of the tumors.

One patient in this series had been treated elsewhere with irradiation therapy, 4,000 roentgens tumor dose, without any decrease in the size of the tumor. If roentgen therapy is of any value, this amount should be adequate; however, in this patient, who received the treatment one year previous to operation, the irradiation served only to hinder surgical removal of the tumor. In the two cases in this series in which malignant transformation was shown by histologic study and invasion of the sternomastoid muscle, deep x-ray therapy was used following surgical excision, and radical neck dissections were carried out as additional precautions. It is my opinion that if the tumor is not malignant and cannot be removed without sacrifice of the common or internal carotid artery, roentgen therapy is preferable to the sacrifice of these major vessels because of the high mortality associated with their ligation or removal.

SUMMARY

Carotid body tumors are not frequently encountered. Their position may be very high or low in the neck, due to variance in the site of the bifurcation of the common carotid artery. Their diagnosis and pathology are discussed; two of eight cases reported were malignant, as shown histologically and by invasion

of the sternomastoid muscle. The use of preoperative compression of the common carotid artery, anticoagulants, and good surgical technique permit most of these tumors to be removed without mortality, and with low morbidity rate.

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AUTOGENOUS VEIN GRAFTS IN SPLENORENAL ANASTOMOSIS

A Description of Technique and Its Clinical Application in Seven Patients

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THE portents of uncontrolled gastrointestinal bleeding in portal hypertension have become increasingly manifest in recent years. This has been the result of careful study of the life expectancy of large numbers of patients.[1-3] Bleeding from esophageal varices or other submucosal veins is potentially a very malignant condition. Thus, 50 to 80 per cent of these individuals will die of hemorrhage within 18 months of the first bleeding episode.

The serious nature of this type of bleeding, and the failure of splenectomy alone to control it,[4, 5] has stimulated a continued interest in its surgical management.

Whipple and his Spleen Clinic group[6, 7] led the way in demonstrating the feasibility of venous shunts as a method of reducing venous pressure in the portal system and thereby diminishing the threat of fatal hemorrhage in portal hypertension. Although the surgery of portacaval shunts, either direct portal vein to inferior vena cava or splenic vein to left renal vein, is still in the developmental phase, the results of this type of surgery have been encouraging. Reports from the few workers concentrating on this problem have demonstrated a significant salvage rate. Although the mortality rate of the operation is gradually falling[8-10] (from 23 per cent to 9.3 per cent) and although 60 to 70 per cent of these patients no longer bleed, both the operative mortality and the cure rate are, I believe, susceptible of further improvement.

In an analysis of our late failures (i.e., recurrence of gastrointestinal bleeding) in the shunt operation, the prime cause has been the early or late obliteration or stenosis of the anastomotic stoma, as confirmed by post-mortem examination. Several hypotheses can be advanced to explain this phenomenon and the most important include (1) disturbances of the clotting mechanism, (2) vascular intimal injury at operation, (3) the technique used in the performance of the anastomosis, and (4) late fibroplasia of the vessel wall. The bugbear of infection that plagued the pioneers in vascular surgery has, of course, been almost overcome by the use of antibiotics. In none of our late closures did we believe thrombus formation a precursor to the stomal closure.

Hoping to modify two of the factors (2 and 3), it was decided to use a free vein graft in selected cases to bridge the gap between the splenic vein and the left renal vein.

HISTORICAL

The experiments of Carrel, and later of Watts, at the turn of the century first demonstrated the feasibility of the use of vein grafts to replace arterial defects. The frequency of infection and secondary hemorrhage delayed the

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clinical application of this basic work. The discovery of antibiotics and the development of improved suture materials have increased the scope of, and successes attained in, this field of vascular surgery.

Much work has been done in the use of arterial grafts, both fresh and preserved, in certain lesions of the cardiovascular system. Southwick[11] attempted to use preserved arterial homografts in experimental portacaval anastomoses in normal dogs. He reported that whereas the operation is technically possible, one-third of his animals developed gradual to complete occlusion of the stoma, and concluded that arterial homografts are unsatisfactory segments for use in this operation. However, arterial grafts are not always practical and this is well summarized by Johnson and co-workers:[12] "The great advantage of vein grafts over artery grafts is that suitable vein can be removed from the patient being operated upon, without serious risk of circulatory insufficiency, whereas an artery of a size suitable for grafting cannot be removed safely. An artery graft must, therefore, have been secured in advance and properly stored." Homologous grafts, either arterial or venous, also pose certain other fundamental problems which will not be included in this discussion.[13]

Autogenous vein grafts have successfully been used in human beings to bridge arterial defects following excision of aneurysm or arteriovenous fistula.[14, 15] More recently, Fontaine and co-workers[16] have advocated the use of vein grafts in arteriosclerosis obliterans.

Johnson and his co-workers[12] in animal experiments successfully transplanted sections of inferior vena cava in aortic defects, surgically produced. Such autogenous vein grafts were uniformly successful and functioned well. Even though a vein was interposed in the major arterial circuit, the high arterial pressure produced only minimal dilatation of the graft in periods up to 14 months postoperative and there was no evidence of aneurysm formation. The grafts were not occluded in any of the experiments. Encouraged by these laboratory results, these workers then used free vein grafts in two patients with the tetralogy of Fallot, bridging the defect between subclavian artery and pulmonary artery with a vein graft obtained from the superficial femoral vein.

Recently McAllister and co-workers[17] reported the experimental use of free vein grafts in revascularization of the heart for deficient coronary circulation. These workers, extending Beck's experiments, used a segment of jugular vein to anastomose the side of the aorta to the coronary sinus. The rate of patency of these vein grafts in 47 animals was 65 per cent. This percentage of patency of the grafts did not approach the 100 per cent figure of Johnson and associates but one must consider that McAllister was using very small caliber vessels of only 3.5 to 4 mm. in diameter, whereas Johnson's vena cava grafts presented a diameter greater than the abdominal aorta in every instance.

Julian and Fildes[18] allude to a single experience in which they performed a portacaval shunt using a femoral vein graft, but did not record the duration of the follow-up.

CLINICAL APPLICATION OF AUTOGENOUS VEIN GRAFTS IN SPLENORENAL SHUNTS

In most primary procedures, I prefer the operation of combined splenectomy and splenorenal shunt to the anastomosis of portal vein to inferior vena

cava.[8-10, 19] Both procedures are arduous and time-consuming operations. Using the usual technique of splenorenal shunt with preservation of the kidney, extreme care must be exercised in the mobilization of the splenic vein preparatory to its use. In comparatively few cases can the splenic vein be used without first freeing up a long segment. At least 8 cm. of the vessel must usually be mobilized proximal to the bifurcation of the hilar branches. This mobilization of the splenic vein involves the division of the left gastroepiploic vein as it enters the splenic vein and the meticulous transfixion of the small pancreatic branches as the splenic vein is followed into the pancreatic substance (Fig. 1). The frequent

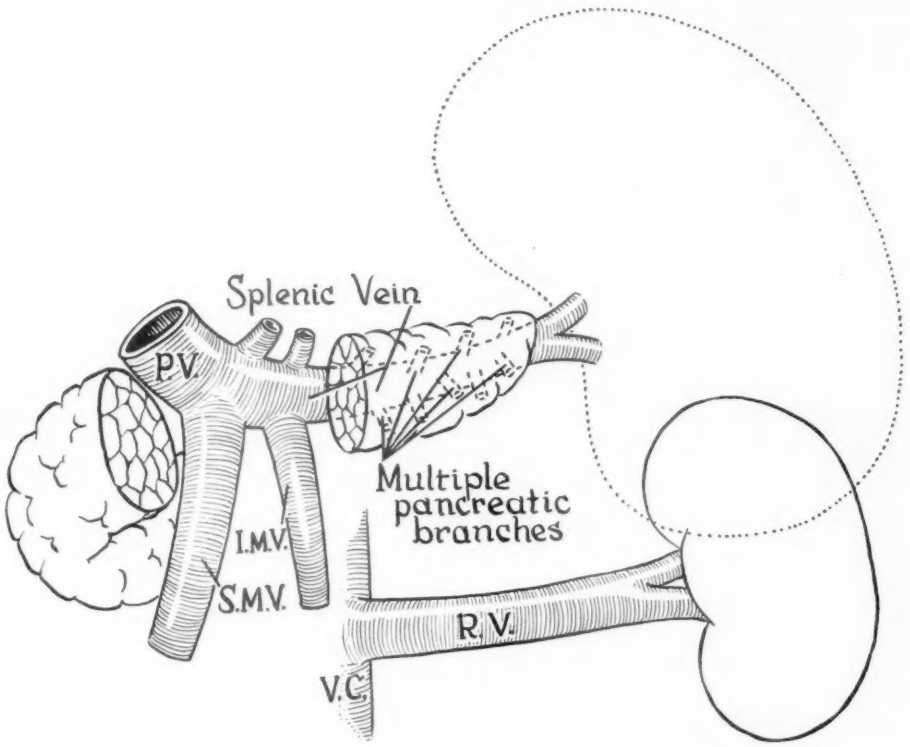


Fig. 1.—Schematic drawing of splenic vein depicting short segment of main vein between tail of pancreas and bifurcation of vein; also multiple pancreatic branches. Use of vein graft obviates ligation of these branches and time consuming mobilization of vein segment as in usual splenorenal shunt operation.

variations of the venous channels in and around the pancreas increase the surgeon's difficulties.[20, 21] Such a dissection is tedious and fraught with the constant danger of tearing the vein wall or of other injury to the vein intima. Even after what appears to be adequate freeing of the splenic vein, the anastomosis of the splenic vein to the left renal vein is still a technically difficult process in most cases and angulation of the splenic vein over the tail of the pancreas or tension of the suture line may occur.

The use of a free vein graft obviates the dissection of the splenic vein out of the pancreatic tissue. Minimal freeing of the vein is necessary, as division of the vessel can be accomplished very close to the hilum of the spleen. Furthermore, the vein graft, because of its length and innate elasticity, seems to automatically adjust itself to the gap between the divided splenic vein and the left

renal vein when it is interposed in the newly created circuit. The method of obtaining the autogenous graft will be described shortly. Suffice it to say that the available vein graft in situ usually measures 5 to 6 cm. With excision of the graft from the donor vein, the segment immediately contracts to approximately half its former length. However, when the graft is subsequently sutured in its new position, its normal elastic qualities are a valuable asset in tailoring it to fit easily and without any tension.

TECHNIQUE

Details of the entire operation will not be included. The technical description will stress those features which are believed to be important in this procedure. The clinical application of a free vein graft in splenorenal shunts was first successfully initiated in St. Vincent's Hospital in May, 1950.

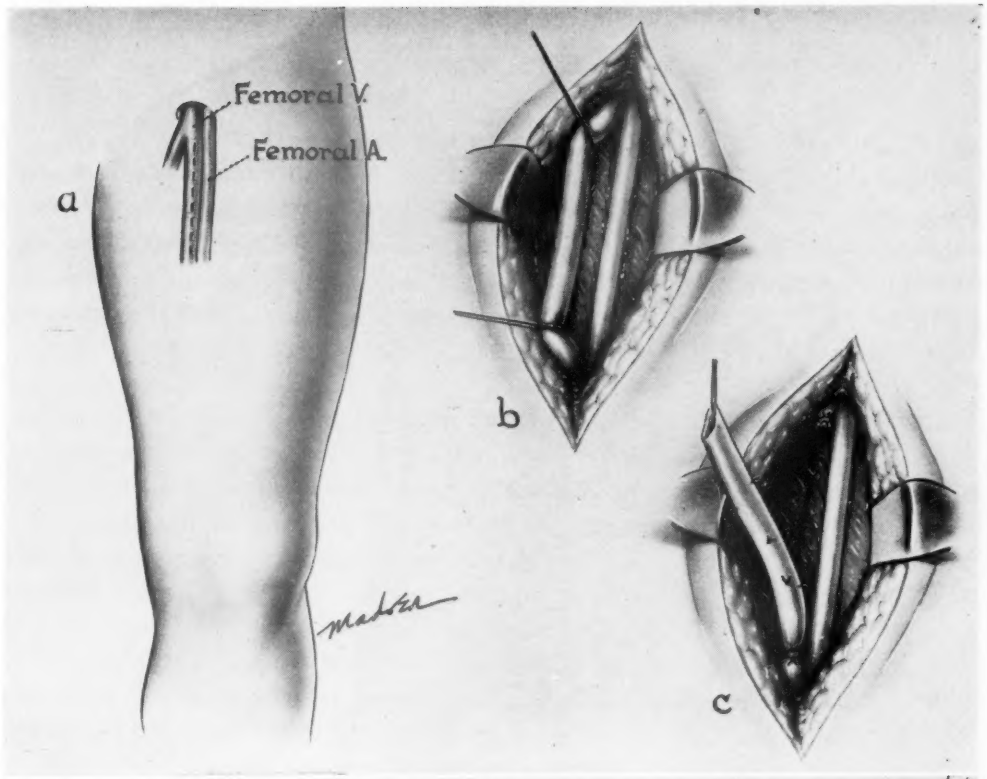
With the patient in the left lateral position for the standard thoracoabdominal approach, two operative fields are simultaneously prepared and draped: (1) the main left thoracoabdominal field, and (2) the donor area over the left femoral triangle.

An auxiliary team of two surgeons obtains the vein graft while the principals begin the main thoracoabdominal incision.

The donor vein (left superficial femoral) is exposed via a 12 to 14 cm. incision starting just below Poupart's ligament and paralleling the course of the femoral vessels. The superficial femoral vein is exposed and a segment is freed, reaching from just distal to the entrance of the saphenous vein down to the profunda vein. Perforating muscular and lateral branches are carefully transfixed with 0000 or 00000 silk close to the vein graft, and clamped and divided distal to the sutures. In most cases a segment of vein graft 5 to 6 cm. can easily be procured (Fig. 2). The proximal and distal ends of the vein, at the extremities of the graft, are doubly ligated with 000 silk (one suture is a transfixion suture). The vein graft is then excised after sharply dividing its proximal and distal ends from the parent vein. No ligation of the ends of the graft is done. The excised graft on removal is flushed with a heparin saline solution and stored in a similar solution in a sterile Petri dish, to await its use by the surgeon. Just prior to removal of the graft it is important to tab proximal or distal end so as to establish its physiologic direction of flow in case the segment contains a valve.[22] This must be known to the surgeon so that it may be correctly interposed in the new circuit. The donor wound is then closed in layers using interrupted silk sutures.

The main team will usually have exposed the spleen by the time of completion of the femoral wound suture. After mobilization of the spleen, its artery is ligated and identification and separation of the secondary splenic veins is begun and their course traced to the bifurcation of the main splenic vein trunk. This portion of the procedure is relatively easy as the splenic vein must only be mobilized for a short distance proximal to its bifurcation. The use of the free vein graft obviates the necessity for the time-consuming dissection into the pancreas, not to mention minimizing injury to the main vein. The details of the use of the free vein graft are illustrated in Fig. 3.

Fig. 2.



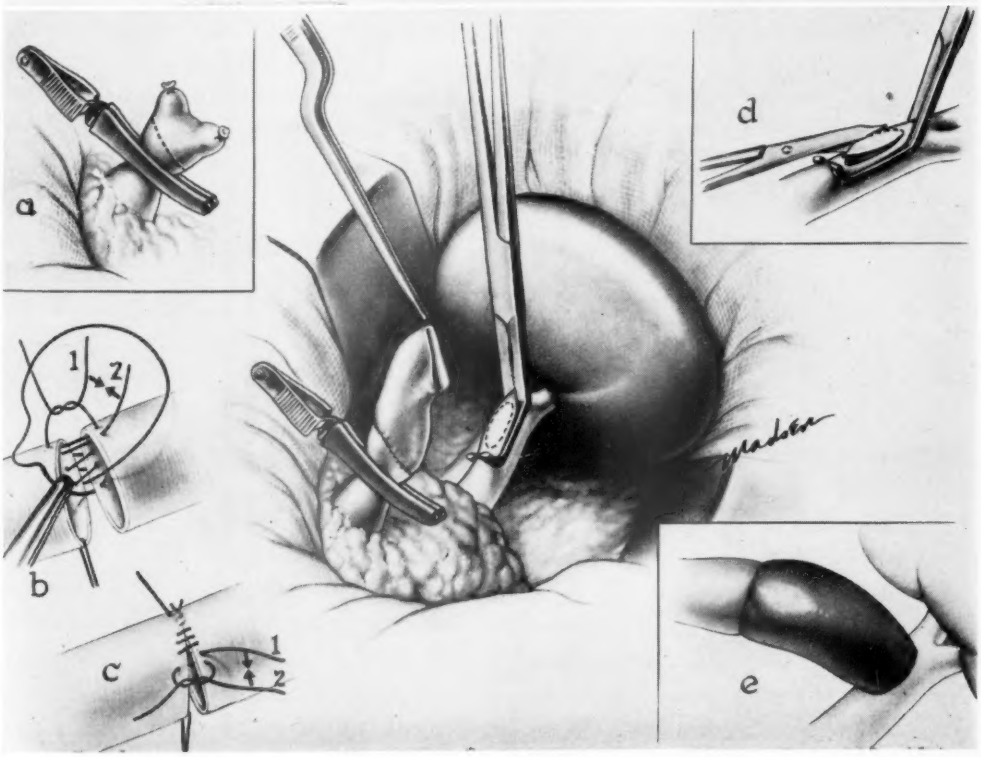


Fig. 3.

Fig. 2.—Location of donor site of autograft. Proximal and distal ends of vein graft must be carefully identified so that graft is properly interposed in the new circuit. The normal superficial femoral vein almost always contains valves at this level (cf. Powell and Lynn[22]).

Fig. 3.—*a*, Stump of splenic vein with serrefine clamp in situ. Dotted line indicates level of oblique section of vein. *b*, (*1*) Initial "stay" suture, (*2*) beginning continuous over-and-over suture of posterior row. *c*, (*1*) Continuous suture drawn taut, preparatory to its fixation to second "stay" suture. *d*, Cutting of oval opening in side wall of left renal vein. *e*, Appearance of interposed vein graft between end of splenic vein and side of left renal vein.

Center drawing.—Relation of graft sutured to end of splenic vein, prior to cutting oval opening in side of renal vein and completion of suture of end of vein graft to side of renal vein; same suture technique is used as illustrated in *b*, and *c*.

TABLE I. RESULTS FOLLOWING USE OF FREE VEIN GRAFTS IN SPLENORENAL SHUNTS

CASE	SEX	AGE	OBSTRUCTIVE FACTOR	TYPE OF OPERATION	HOSPITAL COURSE	FOLLOW-UP	
1	M	49	Laënnec's cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Uncomplicated	Excellent	12 mo.
2	M	36	Vaccine hepatitis and cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Uncomplicated	Recurrent Icterus	4 mo.
						Recurrent Hematemesis	5 mo.
						No further bleeding	9 mo.
3	M	52	Laënnec's cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Pleural effusion (sterile)	Excellent	7½ mo.
4	M	9	Cavernomatous transformation portal and splenic vein	Postsplenectomy* shunt (superior mesenteric to inferior vena cava with graft)	Hematemesis 2nd PO day	Excellent	6½ mo.
5	M	52	Laënnec's cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Pleural effusion (sterile)	Excellent†	5½ mo.
6‡	M	47	Laënnec's cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Died 19th day Dicumarol poisoning	Post-mortem: graft patent, no thromobosis	–
7	M	54	Laënnec's cirrhosis	Splenectomy and shunt (splenic to renal with graft)	Uncomplicated	Excellent	3 mo.

*Splenectomy 14 months prior to the shunting operation.
†No further hematemesis; patient developed moderate edema of leg from which vein graft was taken.
‡Only patient in series to receive postoperative anticoagulant therapy.

The illustrations indicate the greater facility given the surgeon in the progress of his anastomosis. This increased ease of operation significantly shortens operative time, lessens vein trauma, and minimizes blood loss. All these are not inconsiderable factors, I believe, in lowering morbidity and, it is expected, in lessening the incidence of the few late failures of shunting procedures due to stenosis or atresia at the anastomosis.

RESULTS

A shunting operation has now been performed in seven cases, utilizing an autogenous vein graft to bridge the gap between the portal system and the caval system in portal hypertension. The more important details pertaining to these cases are summarized in Table I. In six of these cases, the operation of combined splenectomy and splenorenal shunt was performed, anastomosing the end of the plenic vein to the end of a free vein graft; and, in turn, the other end of the vein graft was sutured to the side of the left renal vein. The additional case was a patient with postsplenectomy bleeding, and the obliterated stump of the splenic vein was, therefore, not usable. A large distended superior mesenteric vein was available. This was dissected free for a few centimeters distal to its lowest arcade. After dividing the superior mesenteric vein in this region, a vein graft was interposed between the end of the superior mesenteric vein and the side of the inferior vena cava, the anastomotic site being inferior to the third part of the duodenum. The latter procedure involved an end-to-end anastomosis of the superior mesenteric vein to the autogenous vein graft and, in turn, the suture anastomosis of the end of the vein graft to the side of the inferior vena cava (Case 6).

The only patient to receive anticoagulant therapy was the single patient who died in the hospital. He was fully ambulatory when, on the thirteenth day, he started to bleed into the intestinal tract and, in spite of all combative measures, succumbed to Dicumarol poisoning. At post-mortem the graft was patent, revealing no narrowing at the two stomas, and normal healing across the suture lines.

The remaining six cases have survived from three to twelve months following operation. It is presumed, but as yet not proved, that healing of the graft has occurred in all cases without secondary infection or dehiscence of the sutured graft. Five of the six patients who survived have had excellent clinical courses with no recurrence of hematemeses for twelve months, in the case followed longest, to three months in the most recent case. The one case, in the survival group with a poor result was that of a patient who developed a recurrence of hepatitis with severe jaundice four months after operation, and one month later had a recurrence of massive hematemesis.

One can only hazard a provisional appraisal of these cases after such a short follow-up.

This preliminary report is, therefore, presented to indicate the feasibility of the operation and its usefulness in shortening operative time and minimizing vessel trauma in portacaval shunts for portal hypertension.

SUMMARY AND CONCLUSIONS

1. Seven cases are reviewed in which autogenous vein grafts were utilized in performing venous shunts between the portal and the caval systems.

2. Salient features of the operative technique are illustrated.

3. The results following operation are summarized.

4. Besides shortening operative time, I believe the facility in performing the vessel anastomosis lessens intimal trauma and thereby may lessen the late complications of stenosis, "webbing," or atresia at the anastomotic ring.

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EXPERIMENTAL STUDIES WITH INTRA-ARTERIAL TRANSFUSION

Overtransfusion of the Normal Dog

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THIS paper reports a study of normal dogs given overtransfusions of whole blood into an artery. The effects of the speed of transfusion and the volume of blood overtransfused into an artery have not been previously studied.

Intra-arterial transfusion in the treatment of hemorrhagic shock was shown to be superior to intravenous transfusion by Kohlstaedt and Page, in 1943. They advised two precautions. They stated that the infused blood should be at a pressure not greater than 150 mm. Hg if the animal were in severe hypotension. They also advised that the venous pressure should be used as a guide to the proper rate of speed of the transfusion. If the venous pressure rose 5 cm. of water or more, the transfusion should be slowed or stopped. In writing about the treatment of shock with intra-arterial transfusion, in 1947, Page stated that if the pressure were raised too high, signs of overtransfusion might appear. If the pressure were raised step-wise in increments of 20 mm. Hg, the restoration of pressure was rapid and without untoward incident.

Porter and his co-workers, in 1948, studied the factor of rate of transfusion with particular reference to the intra-arterial route. They reported that even with rapid transfusion they could not get the systolic pressure to rise more than 20 mm. Hg above its normal value. Congestive heart failure did not occur in fifteen dogs in hemorrhagic shock where the blood withdrawn was put back in rapidly. In treating human surgical patients with excessive blood loss, these authors used up to 500 c.c. of blood in three minutes with 250 to 300 mm. Hg pressure with no untoward effect.

Robertson and his co-workers, in 1948, studied blood flow with the plethysmograph in dogs in hemorrhagic shock. They found that animals bled into hemorrhagic shock would have normal blood flow through the extremities re-established in four to seven minutes if the blood was replaced into an artery. However, if the blood was given intravenously, it took four times longer for the animal to recover than with intra-arterial blood, and the blood pressure and blood flow tended to remain lower after the transfusion was completed.

Pierce and co-workers, in 1949, reported studies with ultra-rapid intravenous blood transfusions in human patients losing large amounts of blood during surgery. They also reported studies with overtransfusion of normal dogs with blood given intravenously. They described five experiments done on dogs weighing from 12.8 to 22.7 kilograms. From their data we have calculated that they

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gave approximately 100 per cent, 135 per cent, 115 per cent, 200 per cent, and 65 per cent increases in blood volume to these five animals in, respectively, 22, 22, 13.5, 19, and 9 minutes. The first three dogs lived, the fourth dog died three minutes after the transfusion, and the fifth dog died immediately. They concluded that the rapid administration of blood to the human patient undergoing surgery was safe. From their data we conclude that in the overtransfusion of the normal dog there are some discrepancies in what a normal animal may receive safely.

Jones and co-workers, in 1950, studied physiologic mechanisms of intra-arterial transfusion, and showed by Diodrast injections that in animals where the systolic blood pressure was under 30 mm. Hg, blood instilled in the femoral artery filled the coronary arteries.

Holden and co-workers, in 1950, studied the myocardial intolerance to excessive blood transfusion. Their animals had no blood lost and were given varied amounts of blood intravenously. They divided their animals into three groups. The first group consisted of five normal intact animals. The second group had small infarcts in the myocardium produced by ligating a branch of the coronary artery a month previously. The third group consisted of five animals who had large myocardial infarcts produced by ligation of a larger coronary artery one month before. The normal group received approximately 97 c.c. of blood per kilogram at the rate of 33 c.c. per minute. From our calculations, this would mean that the animals received approximately a 135 per cent increase in blood volume. Of these animals, two were killed by the investigators, one died within 24 hours, and the authors reported that two recovered. In the small infarct group, the animals received approximately 164 c.c. of blood per kilogram body weight at the rate of 69 c.c. per minute. We calculate that this represents an increase in blood volume of more than 235 per cent. The authors reported that this group lived, but that the animals were all killed immediately after transfusion for autopsy. In the large infarct group, the animals received 181 c.c. of whole blood per kilogram body weight, which we calculate to represent nearly a 260 per cent increase in blood volume. The authors reported that all these animals died. Their conclusion from these experiments was that overtransfusion, especially if there were any myocardial insufficiency, was dangerous.

Intra-arterial transfusions have come to be used very frequently in resuscitating patients with severe hemorrhagic shock. It has also been suggested that intra-arterial transfusions might be of benefit in nonhemorrhagic shock, as, for example, in the shock from myocardial infarction or a severe pulmonary embolus. We have used intra-arterial transfusions in these conditions with varying results. Our cases are not numerous enough to comment upon at this time. There are theoretical problems raised when any considerable amount of whole blood is given to a subject in shock not caused by blood loss. How much blood can be given? How fast can the blood be given? In the experimental approach to this problem, we decided to study in the intact animal how much overtransfusion could be given intra-arterially, and to study some of the physiologic changes in the overtransfusion of the intact animal with intra-arterial blood. This paper describes our experiences with this problem.

METHODS

Thirty healthy mongrel dogs of both sexes, varying in weight from 4 to 10 kg. were transfused with whole blood. All animals were anesthetized with intravenous Nembutal. They were given an initial dose of approximately 25 mg. of Nembutal per kilogram body weight and were given supplementary doses in small amounts to maintain light anesthesia. Citrated blood was collected aseptically from donor dogs into standard transfusion flasks and stored from one to seven days in a refrigerator at 4° C. Four groups of dogs were used. In Group I, there were no aseptic precautions used other than that the blood administered through the system was sterile. The right jugular vein was used to measure venous pressure by means of a saline manometer. The right femoral artery was used for infusion of the intra-arterial blood, and the left femoral artery was used for a cannula through which the arterial blood pressure could be measured by means of a Sanborn electromanometer. At the conclusion of the transfusion experiment in this group of animals the jugular vein, right femoral artery, and left femoral artery were ligated. In the Group II Experiments, the animals were also subjected to transfusion with no aseptic precautions. However, the right femoral vein was used instead of the jugular vein to measure venous pressure, and at the conclusion of the experiment the right femoral vein and both femoral arteries were ligated. In the Group III animals, again aseptic precautions were not used, however, no vessels were sacrificed. The venous and arterial pressures were not measured. The transfusion was given through a needle puncturing the femoral artery. At the conclusion of the experiment, the needle was withdrawn, hemostasis was obtained by temporary pressure applied through the artery, and no vessels were ligated. In the Group IV experiments, aseptic precautions were used. Sterile blood and sterile transfusion systems were employed. The blood was infused through a puncture into the femoral artery. At the conclusion of the experiment no vessels were ligated.

GROUP I EXPERIMENTS

Ten animals received transfusions varying from a 38 per cent increase in blood volume to a 130 per cent increase in blood volume. These calculations were based on the premise that the blood volume of the normal dog was approximately 7 per cent of his body weight. The transfusions took from 2.5 to 65 minutes to administer. Of these ten dogs, seven died within 24 hours after the transfusion. Three animals lived and seemed to recover uneventfully. During the experiments, some animals developed muscle twitchings, and if they regained consciousness seemed to be dazed and confused. Many did not regain consciousness and seemed to die from cerebral congestion. Therefore we decided to continue these experiments, but not to use the jugular vein.

GROUP II EXPERIMENTS

Seven animals received transfusions which increased their blood volume from 25 per cent to 100 per cent. They received these transfusions at speeds varying from 2.5 to 60 minutes. All animals but one survived. One animal received 100 per cent overtransfusion in thirty minutes and died the next day.

GROUP III EXPERIMENTS

Five animals received overtransfusions varying from 50 per cent to 100 per cent increase in blood volume. The blood was administered in varying amounts of time, from 28 to 59 minutes. Four animals survived; one animal receiving a 71 per cent increase in 28 minutes died during the experiment.

EFFECT OF VARYING THE RATE OF TRANSFUSION

1. Slow Transfusion.—There were eleven animals in this group who received slow transfusions. Five of the eleven were Group I animals, two of the eleven were Group II animals, and four of the eleven were Group III animals. These results have been summarized in Table I. In the Group I animals, only one animal survived the transfusions. The two animals in Group II and the four animals in Group III all survived their overtransfusions which varied in amount from 50 per cent to 100 per cent, administered in 30 to 60 minutes. It is probable that the poor results in Group I were due to ligation of the jugular vein, but it would seem that most intact animals tolerate transfusions of 50 per cent to 100 per cent increase in blood volume in 30 to 60 minutes.

2. Moderate Speed Transfusion.—Six animals were in this series. Four of the animals were Group I animals, one was a Group II, and one was a Group III animal. Two of the Group I animals survived and two died. The one Group II and the one Group III animal died. These animals received a 50 per cent to a 120 per cent increase in blood volume in 18 to 35 minutes. The data suggest that at a faster rate of administration, excess blood is less well tolerated. The results have been summarized in Table I.

TABLE I. EFFECT OF RATE OF OVERTRANSFUSION

RATE	TYPE OF EXPERIMENT	APPROXIMATE BLOOD VOLUME INCREASE (IN PER CENT)	TIME FOR THE BLOOD TRANSFUSION (IN MINUTES)	FATE OF THE ANIMAL
Slow	Group I	62	38	Died
	I	50	34	Lived
	I	50	23	Died
	I	130	65	Died
	I	120	50	Died
	Group II	100	60	Lived
	II	100	60	Lived
	Group III	50	30	Lived
	III	50	30	Lived
	III	100	60	Lived
	III	90	52	Lived
Moderate	Group I	60	19	Died
	I	50	18	Lived
	I	50	18	Lived
	I	120	35	Died
	Group II	100	30	Died
	Group III	71	28	Died
Fast	Group I	35	2.5	Died
	I	80	4	Died
	Group II	25	4	Lived
	II	25	3	Lived
	II	31	4.5	Lived
	II	33	2.5	Lived

3. Fast Transfusion.—In this group there were six animals: two from Group I and four from Group II. Both the Group I animals died following transfusions of 35 per cent increase and 80 per cent increase administered in 2.5 and 4 minutes. The Group II animals all survived transfusions varying from 25 per cent to 33 per cent increase administered in 2.5 to 4.5 minutes. From this we concluded that small transfusions in the order of 25 per cent to 35 per cent increase in blood volume were tolerated even at very rapid speeds of 2 to 4 minutes. These results are summarized in Table I.

INTRAVENOUS OVERTRANSFUSION

Four animals were in this group. The blood was transfused into the left femoral vein. The left femoral artery was ligated in all four animals. In two animals, the right jugular vein was ligated, and in two animals the right femoral vein was ligated. These four animals received overtransfusions varying from 34 per cent to 105 per cent in 2.5 to 54 minutes. One animal which had the right femoral vein ligated rather than the right jugular vein was the only animal to survive. It seems that the changes produced by the overtransfusion were the same in this intravenous group as in the intra-arterial overtransfusion group.

INTRA-ARTERIAL OVERTRANSFUSION TREATED WITH PHLEBOTOMY

The results are summarized in Table II. There were five animals in this group. The animals received overtransfusions into the left femoral artery. The blood was removed from the jugular vein. The right jugular vein, left femoral artery, and the right femoral vein were all ligated at the conclusion of the experiment. These animals received from 100 per cent to 225 per cent increase in blood volume during 35 to 58 minutes. Blood was removed by phlebotomy, varying in amount from 45 per cent to 140 per cent of the blood volume in 12 to 46 minutes. The phlebotomy was done either at the end of the overtransfusion or simultaneously with the overtransfusion. The animals had a net gain in blood volume varying from 35 per cent to 85 per cent in a total of 46 to 78 minutes. All these animals died. Withdrawing the blood after an overtransfusion had been produced did not save any animal.

TABLE II. INTRA-ARTERIAL OVERTRANSFUSION TREATED WITH PHLEBOTOMY*

ANIMAL NUMBER	APPROXIMATE BLOOD VOLUME INCREASE; TIME FOR TRANSFUSION	APPROXIMATE BLOOD VOLUME DECREASE BY PHLEBOTOMY; TIME FOR PHLEBOTOMY	GAIN IN VOLUME; TIME FOR TRANSFUSION AND PHLEBOTOMY	FATE OF ANIMAL
15	100% in 35 min.	50% in 20 min.	50% in 55 min.	Died next day
16	100% in 60 min.	45% in 12 min.	55% in 72 min.	Died next day
17	100% in 58 min.	65% in 20 min.	35% in 78 min.	Died 30 min. later
8	120% in 51 min.	65% in 17 min.	55% in 68 min.	Died next day
7	225% in 46 min.	140% in 46 min.	85% in 46 min.	Died next day

*Blood transfused into left femoral artery. Blood removed from jugular vein. Right jugular vein, left femoral artery, and right femoral vein liga ed.

SURVIVAL RATE AFTER 100% INCREASE IN BLOOD VOLUME IN 30 TO 60 MINUTES

Ten animals of Groups II, III, and IV were used. These results are tabulated in Table III. These animals received approximately 100 per cent increase in their blood volume. The time of administration varied from 30 to 60 minutes. Seven animals lived, three died either immediately or within 24 hours after transfusion. The animals that died received their 100 per cent increase in blood volume in 30 minutes. It is probable that 100 per cent increase in blood volume in 30 minutes is not more lethal than 100 per cent increase in 60 minutes since the physiologic changes in the 30 minute and 60 minute transfusion dogs seemed about the same. Two other dogs receiving 100 per cent increase in blood volume in 30 minutes survived. It would seem that the mortality rate from overtransfusion with a 100 per cent increase in blood volume given intra-arterially in 30 to 60 minutes is approximately 30 per cent.

TABLE III. SURVIVAL RATE AFTER 100% INCREASE IN BLOOD VOLUME IN 30 TO 60 MINUTES. (70% OF THE ANIMALS SURVIVED.)

EXPERIMENT NUMBER	TYPE OF EXPERIMENT	INCREASE IN BLOOD VOLUME; TIME FOR TRANSFUSION	FATE OF ANIMAL
24	Group II*	100% in 60 min.	Lived
25	Group II*	100% in 60 min.	Lived
26	Group II*	100% in 30 min.	Died 24 hours later
32	Group II*	100% in 60 min.	Lived
29	Group III†	100% in 59 min.	Lived
30	Group III†	90% in 52 min.	Lived
33§	Group IV‡	100% in 31 min.	Died 24 hours later
34	Group IV‡	100% in 30 min.	Lived
35	Group IV‡	100% in 30 min.	Died immediately
36	Group IV‡	100% in 30 min.	Lived

*No aseptic precautions. Right femoral vein and both femoral arteries ligated.
†No aseptic precautions. Femoral artery punctured, but no vessels ligated.
‡Aseptic precautions used. Femoral artery punctured but no vessels ligated.
§Wound contaminated after transfusion in this animal.

EFFECT OF SEPSIS

Nelson, in 1951, reported that dogs given transfusions with contaminated blood were likely to die 24 hours later due to the effects of the paracolon bacillus. Since our experiments had been done without aseptic precautions, we decided to check the results with animals given blood with aseptic precautions through a puncture of the artery with preservation of the integrity of all blood vessels. These animals were designated Group IV. Four of these animals received 100 per cent increase in blood volume in 30 minutes. One animal died immediately, during the transfusion, two animals survived uneventfully, and one animal died 24 hours later. This latter animal received the blood under aseptic precautions, but contaminated the femoral wound with feces at the conclusion of the experiment. The results in these four animals seem similar to the data obtained when blood was not given with strict aseptic precautions.

PHYSIOLOGIC CHANGES DURING OVERTRANSFUSION

Physiologic measurements were made in twenty-six animals while overtransfusions were given. The respiratory rate was counted each minute. The venous

pressure was measured by a saline manometer. The pulse rate and the systemic blood pressure were measured by a Sanborn electromanometer.

The data have been analyzed to determine whether speed of transfusion or percentage increase in blood volume produced significantly different effects in respiratory rate, venous pressure, pulse rate, or systemic blood pressure.

1. Slow Transfusion.—Seven animals were studied in this group. The transfusion speed and volume given to these animals have already been listed in Table I. Fig. 1 portrays the physiologic changes in Animal 24.

Respiratory rate: In one animal, the control rate of 20 per minute fell to 9 per minute after the transfusion. In the other six animals, the average control respiratory rate was 14 per minute. The average rate after the transfusions was 33 per minute.

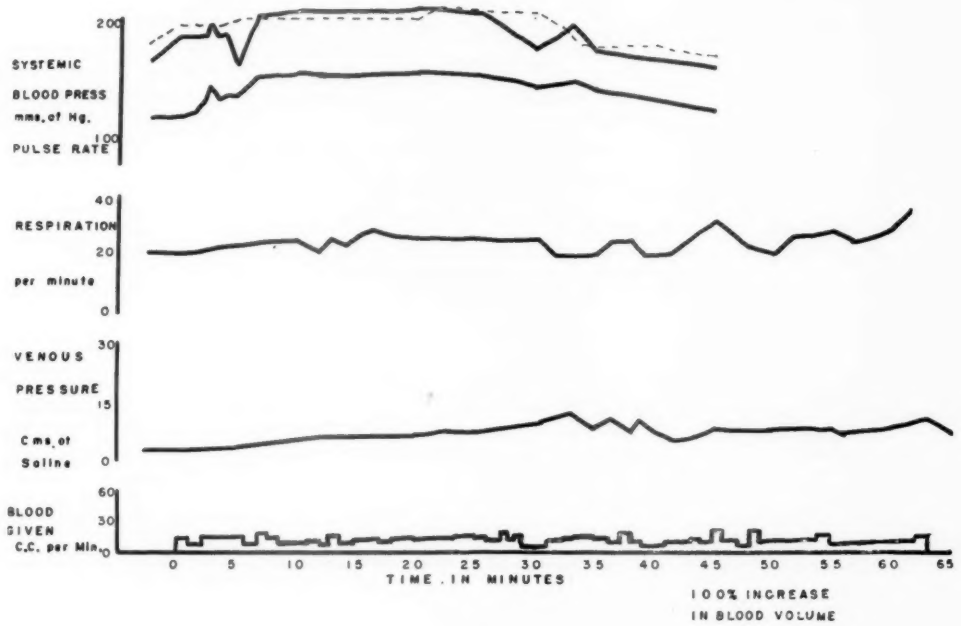

Fig. 1.

Venous pressure: The venous pressure rose in all seven animals. The average rise was 7.1 cm. of saline.

Pulse rate: In one animal the pulse rate increased from a control rate of 180 beats per minute to 240 beats per minute. In the other six animals the average control rate of 160 beats per minute fell to an average rate of 100 beats per minute after the transfusions.

Blood pressure: In all seven animals the blood pressure was significantly lower than normal after the transfusions. In six of the seven animals there was a transitory rise in the blood pressure for a few minutes shortly after the start of the transfusion. The systolic blood pressure seldom rose more than 20 millimeters of mercury above the normal value. In Animal 9 the control pressure of 250/150 rose to 300/180 and then fell to 180/100 at the end of the transfusion.

2. Moderate Speed Transfusion.—Five animals were studied in this group. Table I lists the speed of transfusion and the blood volume increase given each of these animals. Fig. 2 shows the physiologic changes found in Animal 26.

Respiratory rate: The changes in respiratory rates were inconsistent. The rate fell in three animals, stayed the same in one animal, and rose in one animal.

Venous pressure: The venous pressure rose in all animals. The average increase was 8.6 cm. of saline.

Pulse rate: The changes in pulse rate were inconsistent. The pulse rate fell in one animal, was unchanged in one animal, and rose in one animal.

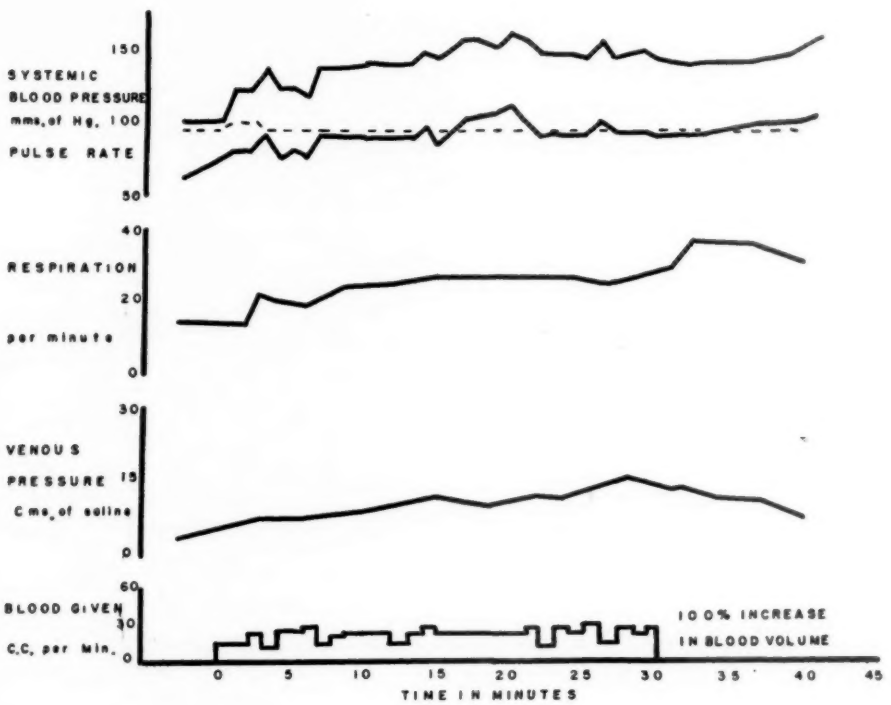

Fig. 2.

Blood pressure: The blood pressure was unchanged in one animal. In one animal the control blood pressure of 100/60 rose to 160/100 after the transfusion. In three animals the blood pressure rose slightly and then fell below normal at the end of the transfusion.

3. Fast Transfusion.—Six animals were studied in this group. Table I shows the speed of transfusion and the blood volume increase given to each of these animals. Fig. 3 shows the physiologic changes in Animal 20.

Respiratory rate: One animal died immediately. In the other five animals the average respiratory rate of 13 per minute rose to an average rate of 24 per minute at the end of the transfusions.

Venous pressure: In all six animals the venous pressure rose. The average rise was 21 cm. of saline.

Pulse rate: One animal died. In four animals the pulse rate remained nearly constant throughout the transfusions. In one animal the pulse rate slowed from 190 beats per minute to 160 beats per minute.

Blood pressure: In one animal the control blood pressure was 150/120 and rose to 180/140 at the end of the transfusion. The blood pressure fell without a transitory rise in the other five animals.

The physiologic changes may be summarized as follows: In these experiments the changes seemed to be more closely related to rate of administration than blood volume increase. The respiratory rate rose in twelve of eighteen

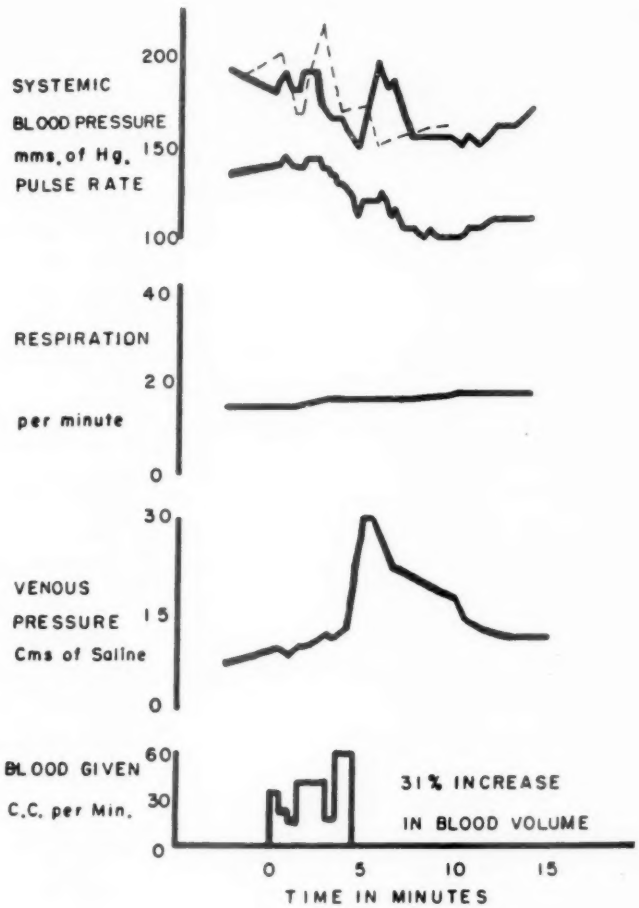

Fig. 3.

animals. The venous pressure rose in all eighteen dogs. The most marked increases in venous pressure occurred in the fast transfusions. This is epecially significant when it is noted that this group received the smallest increments in blood volume. It seems particularly important to note that the venous pressure rose in every experiment, but that in every experiment the venous pressure had fallen nearly to normal 5 to 10 minutes after the end of the transfusion. The changes in the pulse rate were inconsistent. Eight of the fifteen animals developed slower pulse rates with the transfusions. In fourteen of the eighteen

animals the blood pressure fell significantly during the transfusions. In the slow and moderate transfusions, nine of twelve animals developed a transitory hypertension at the start of the transfusion. In the six animals receiving fast transfusions, five did not show any transitory rise in blood pressure.

PATHOLOGIC CHANGES

There appeared to be two mechanisms of death from overtransfusion. If a transfusion was given at a very rapid rate, acute heart failure and death were likely to occur in a very few minutes. If the transfusion was administered more slowly and if large volumes of blood were given, the animal died either from cardiac failure or from what appeared to be cerebral damage from plethora. Of the dogs in this series that died 24 hours later, most never regained consciousness. The animals exhibited fibrillar twitchings and signs of decerebration. One animal that survived was very ataxic and staggered around his cage.

Post-mortem examination of the overtransfused animals showed an enlarged, dilated heart, markedly engorged viscera, and hemorrhagic fluid in the serous cavities.

SUMMARY

1. Overtransfusions of whole blood were given into the femoral artery of normal dogs.

2. The percentage increase in blood volume and the speed of transfusion were found to be major factors in the survival of the animal.

3. When an increase in blood volume of approximately 100 per cent was given in 30 to 60 minutes, the mortality rate was 30 per cent.

4. The animals survived an overtransfusion of 25 per cent to 35 per cent of their blood volume given in 4 to 5 minutes.

5. The effect of overtransfusion upon respiratory rate, venous pressure, pulse rate, and blood pressure are described.

6. The venous pressure reflected an overtransfusion. In these experiments the venous pressure returned to normal levels 10 to 15 minutes after the transfusions were completed.

7. Animals died either from acute cardiac failure or from signs of plethora and cerebral damage.

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SPINAL ANESTHESIA

Analysis of Causes of Death in 716 Cases

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AN ANALYSIS of the causes of death in the fatalities among 580 patients in 716 successive spinal anesthesias over an eighteen-month period is presented.

In this series of spinal anesthesias twenty-six deaths from all causes occurred during the hospital stay of the patients. This is an over-all mortality of 3.63 per cent. The deaths occurred from thirty minutes following operation to the fifty-seventh postoperative day. Before entering into a detailed analysis of these deaths, several matters of general interest will be presented.

The anesthetic agents used in this series with the number of deaths and the mortality are presented in Table I.

Table I. Anesthetic Agents

Agent	Number of Cases	Deaths	Mortality (Per Cent)
Pontocaine	380	21	5.5
Pontocaine-procaine 1:10 ratio	238	2	0.84
Procaine, continuous spinal	25	3	12.0
Procaine	58	0	0.0
Nupercaine	15	0	0.0
Total	716	26	3.63

With these 716 spinal anesthesias, 769 surgical procedures were done. Table II shows a recapitulation of this, in more detail, with the number of deaths occurring in each classification.

Table II. Surgical Procedures

	Number	Deaths	Mortality (Per Cent)
General surgery			
Major	145	15	10.3
Minor	151	0	0.0
Urologic surgery			
Kidney	13	1	7.7
Transurethral	321	6	1.8
Suprapubic and perineal	61	2	3.2
Transabdominal	6	0	0.0
Gynecologic surgery			
Vaginal and perineal	20	0	0.0
Transabdominal	23	1	4.3
Cesarean sections	28	1	3.5
Normal deliveries	1	0	0.0
Totals	769	26	3.38

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Complemental anesthesia was used in 100 cases. This can be defined as an additional anesthetic which was included in the original plan of administration. Table III lists the reasons for such inclusion.

TABLE III. COMPLEMENTAL ANESTHESIA

REASON	NUMBER
Upper abdominal surgery and position	82
Patient desired to be asleep during operation	7
Apprehension	5
Severe cardiac (requested by surgeon)	1
Reason not stated	5
Total	100

Supplemental anesthesia was used in 48 cases. This may be defined as an additional anesthetic which it became necessary to use, but which was not included in the original plan of administration. Table IV lists the reasons for its use.

TABLE IV. SUPPLEMENTAL ANESTHESIA

REASON	NUMBER
Inadequate spinal anesthesia	18
Apprehension	8
Restlessness in long operation	7
Sensitive to pressure (bladder distention and/or exploration)	6
Youth of patient	1
Nausea	1
Requested by surgeon	1
Change of operation	2
Reason not stated	4
Total	48

Table V lists the agents used in the foregoing 148 cases and gives the number of deaths and the mortality rate occurring under each.

TABLE V

AGENT	NUMBER	DEATHS	MORTALITY (PER CENT)
Nitrous oxide-oxygen	17	3	17.6
Cyclopropane, oxygen	61	8	13.1
Nitrous oxide, cyclopropane, oxygen	29	0	0
Pentothal Sodium, cyclopropane, oxygen	4	1	25.0
Cyclopropane, ether, oxygen	4	0	0
Pentothal Sodium	32	2	6.2
Local infiltration	1	0	0
Total	148	14	9.4

Complications arising during operation were in no case fatal on the operating table. Table VI lists the complications which occurred during operation.

TABLE VI. COMPLICATIONS DURING SURGERY

1. Cardiovascular	
(a) Blood pressure drop to 80 mm. Hg systolic or below	107
(b) Blood pressure drop of 40 mm. Hg but remaining above 80 mm. Hg systolic	72
(c) Arrhythmias	22
(d) Coronary occlusion	4
(e) Cerebrovascular accident	2
2. Respiratory	
(a) Respiratory depression (high spinal)	9
3. Gastrointestinal	
(a) Nausea and/or emesis	45
4. Miscellaneous	
(a) Severe backache	2
(b) Dizziness	1

Complications in the immediate postoperative period are listed in Table VII.

TABLE VII. POSTOPERATIVE COMPLICATIONS

1. Cardiovascular	
(a) Hypotension	19
(b) Hypertension	7
(c) Arrhythmia (tachycardia, etc.)	27
(d) Shock	3
(e) Hemorrhage	4
(f) Coronary infarction	4
(g) Pulmonary infarction	6
(h) Cerebral embolic accident	2
2. Respiratory	
(a) Pneumonia	1
(b) Cough	1
(c) Pain in chest	2
3. Central nervous system	
(a) Headache	20
(b) Convulsions	1
(c) Confused or irrational	8
4. Gastrointestinal	
(a) Nausea	69

As stated earlier the total mortality rate in this series of 716 cases was 3.63 per cent. Table VIII shows how the deaths were distributed in the various age groups by decades.

TABLE VIII. MORTALITY BY AGE

AGE GROUP	TOTAL CASES	DEATHS	MORTALITY (PER CENT)
10-19	11	0	0
20-29	49	0	0
30-39	53	2	3.8
40-49	85	4	4.7
50-59	113	4	3.6
60-69	197	7	3.5
70-79	164	6	3.65
80-89	41	2	5.0
90-99	3	1	33.3
Total	716	26	3.63

From this table it would appear that age is of little consequence in affecting the total death rate, except in the first two groups where no deaths occurred, and

in the last group where the paucity of cases would make any deaths at all account for the high mortality rate.

The importance of the preoperative evaluation of patients, as arrived at by an appraisal of their physical state, in the determination of the mortality rate is shown in Table IX.

TABLE IX. MORTALITY IN RELATION TO PHYSICAL STATE

EVALUATION	TOTAL CASES	DEATHS	MORTALITY (PER CENT)
ID*	46	3	6.5
E	25	1	4.0
A	104	0	0
B	412	9	2.5
C	121	10	8.2
D	7	3	42.8
DD	1	0	0
Total	716	26	3.63

*Insufficient data for evaluation.

This table would seem to indicate that the standard system of evaluation of patients is fundamentally sound.

Early in the survey it became apparent that there was a relationship between death and hypotensive changes during anesthesia, and between death and those circulatory complications occurring postoperatively. The operative hypotensive conditions fall into three groups.

1. Initial systolic blood pressure of 90 mm. Hg or below.
2. A drop of 40 mm. Hg or more in the systolic blood pressure, but with blood pressure remaining above 80 mm. Hg.
3. A systolic blood pressure drop to 80 mm. Hg or below.

The circulatory changes found in the postoperative period can be seen by consulting Table VII.

There were 179 cases in which one of the above hypotensive changes occurred on the operating table. This is 25 per cent of the total cases. In this group there were 15 deaths. In the postoperative period 65 cases developed circulatory changes. There were 21 deaths in this group. Three deaths occurred in the remaining 510 cases. The apparent discrepancy in the total number of cases and deaths is due to an overlapping of 38 cases in which there were both hypotensive changes during operation and postoperative circulatory changes. In this small group of 38 cases there were 13 deaths with a mortality rate of 34.2 per cent.

From the preceding it will be seen that all of the cases align themselves into four categories:

1. No hypotensive or postoperative circulatory changes, 510 cases.
2. Hypotensive but no postoperative circulatory changes, 141 cases.
3. Postoperative circulatory but no hypotensive changes, 27 cases.
4. Operative hypotension and postoperative circulatory changes, 38 cases.

It became apparent from an analysis of the cases that many deaths were due to conditions unrelated to the anesthetic. In the following discussion of the above 4 categories all deaths which were not of a vascular nature will be eliminated. In the series there are 15 deaths which are frankly vascular in nature.

CATEGORY 1

In this group of 510 cases there were 3 deaths. None of these were from vascular causes, and the cause of death is not related to the anesthetic.

CATEGORY 2

In this group of 141 there were 3 cases in which the initial blood pressure was 90 systolic or below; 54 cases where there was a drop of 40 mm. or more, but where the pressure remained over 80 mm. and 82 cases where the pressure dropped to 80 mm. or below. In this group there were 2 deaths; neither of these was from vascular causes.

CATEGORY 3

In this group of 27 cases there were 9 deaths. This is a gross mortality of 33.3 per cent. Four of the deaths were not of a vascular nature and the cause seemed to be related to the disease from which the patient suffered rather than to the anesthesia.

While there were vascular aspects to the cause of death of 2 patients, it is obvious that these were entirely secondary to, and caused by, the disease from which the patient suffered and were not due to the anesthesia.

The causes of death in 3 cases were definitely major vascular complications. Thus, in this category there were 3 deaths from vascular causes, a mortality rate from vascular causes of 11.1 per cent.

The postoperative circulatory complications occurring in this category are listed in Table X.

TABLE X. CIRCULATORY COMPLICATIONS

COMPLICATION	NUMBER
1. Hypotension	7
2. Tachycardia 100+	13
3. Shock and/or hemorrhage	4
4. Arrhythmias	2
5. Pulmonary infarction	4
6. Cerebral accident	1
7. Hypertension	1

Pulmonary infarction occurred 4 times and cerebral accident once. These were the only major vascular accidents in this category. There were 3 deaths in which these causes were involved; this is a survival rate of 40 per cent.

CATEGORY 4

In this group of 38 cases there were 13 deaths for a gross mortality rate of 34.2 per cent. Twelve of these thirteen deaths were from vascular causes. This

means that of the 15 deaths from vascular causes occurring in the entire series of 716 cases 86.7 per cent occurred in this group.

There were 2 patients in this category with an initial blood pressure of 90 mm. or less. Neither of these died. There were 15 cases in which there was a blood pressure drop of 40 mm. or more, but the minimum pressure remained above 80 mm. There were 2 deaths in this group, both of which were vascular in nature, making a mortality rate of 13.3 per cent. There were 21 cases in which the operative blood pressure dropped to 80 mm. or below. In this group there were 11 deaths, 10 of which were vascular in nature. This is a gross mortality rate of 52.4 per cent or 47.6 per cent from vascular causes.

Since this category contains all of the cases of death not so far eliminated as being nonvascular in nature, only 1 case need be eliminated as being of this type.

In this category there were eleven major circulatory accidents, listed in Table XI.

TABLE XI. CIRCULATORY ACCIDENTS

Fatal hemorrhage	3
Coronary occlusion	5
Pulmonary embolism	2
Cerebral accident	1

There was only one survival in these cases, a patient with a myocardial infarction secondary to coronary occlusion which occurred on the operating table. Infarction was demonstrated by the electrocardiogram. In Category 3 the survival rate from major circulatory causes was 40 per cent while in Category 4 the survival rate had dropped to 9.1 per cent.

Of the 4 cases of fatal hemorrhage occurring in the entire series 3 were in this category.

Severe postoperative hypotension preceded the major circulatory accident in 5 of these cases. In the 1 case of coronary occlusion where survival occurred the hypotension followed the accident. It occurred in all 3 cases of hemorrhage and in the case of cerebral accident.

In the 4 cases of fatal coronary occlusion and the 2 cases of pulmonary embolism there were no other postoperative circulatory complications.

Other circulatory complications which occurred in Category 4 are listed in Table XII.

TABLE XII

COMPLICATION	NUMBER
Severe blood pressure fall on postoperative day	11
Arrhythmias, operative to 7th postoperative day	4
Tachycardia, operative day	8
Postoperative hypertension	7

In the group of 7 cases in which there was a severe postoperative hypertension there were no fatalities.

No deaths occurred in the 4 cases in which the initial blood pressure was below 90 mm. Hg systolic.

In the total series there were 15 deaths from vascular causes. The mortality rate from purely vascular causes for the entire series of 716 cases is 2.09 per cent.

There were 65 cases in which there were major and minor circulatory changes in the postoperative period. As would be expected all of the 15 deaths from vascular causes occurred in this group. The mortality rate from vascular causes in these 65 cases is 23 per cent.

The 27 cases in Category 3 were a portion of this group of 65 cases. As stated above the mortality in this category from vascular causes was 11.1 per cent. This would indicate that the development of circulatory changes in the immediate postoperative period increased the chance of mortality by more than 5 fold.

In this group of 65 cases there were 15 cases in which there was a blood pressure drop of 40 mm. Hg systolic, but where the pressure remained above 80 mm. Hg systolic. There were 2 deaths from vascular causes in this group. The mortality rate for this small group was 13.3 per cent. Since the addition of this complication increases the mortality rate only 2.2 per cent over the mortality rate of Category 3 it must be said that this hypotensive change during operation was of only minor significance.

The critical portion of this group of 65 cases, and the part which accounted for the 23 per cent mortality rate, were the 21 cases in which there was a drop in the systolic blood pressure to 80 mm. Hg or below. In this group there were 10 deaths from vascular causes or 66.7 per cent of all of the vascular deaths. As stated at the end of the discussion of Category 4 this was a mortality of 47.6 per cent.

Eight of these ten patients were over 57 years of age and the group had an average age of 70.5 years.

In an effort to determine whether the presence of preoperative cardiovascular disease might be used in detecting patients likely to fall into Category 4 the entire series was analyzed from this point of view.

The 716 spinal anesthesias were given to 580 patients.

The cardiovascular abnormalities found varied from mild exertional dyspnea to grave cardiac disease proved by the electrocardiograph. Included also were all cases of hypertension of more than 160 mm. Hg systolic. These are classified in Table XIII.

TABLE XIII

PREOPERATIVE CARDIOVASCULAR COMPLICATIONS

1. No cardiovascular abnormalities	240
2. Hypertension	54
3. Cardiovascular abnormalities	286

In Group 1 there was a total of 14 deaths, 7 of which were from vascular causes. The gross mortality rate was 5.8 per cent and the vascular mortality rate was 2.9 per cent. In Group 2 there was 1 death from vascular causes. This makes the gross and vascular mortality rate 1.8 per cent. In Group 3 there was a total of 12 deaths, 8 of which were from vascular causes. The gross mortality rate was 4.1 per cent, and the vascular mortality rate was 2.7 per cent.

From the foregoing it appears that in the patient undergoing spinal anesthesia the presence of pre-existing cardiovascular disease has little or nothing to do with either the gross mortality rate or the mortality from vascular causes.

If any conclusion could be drawn from this small series of cases it would be that the patient with uncomplicated hypertension is a better candidate for spinal anesthesia than either the patient with no cardiovascular disease or the patient with cardiovascular abnormalities.

SUMMARY AND CONCLUSIONS

An analysis of the causes of death in the fatalities among 580 patients in 716 spinal anesthesias has been made.

Complemental or supplemental anesthesia increases the hazard of spinal anesthesia.

Spinal anesthesia is excellent for elderly and poor-risk patients, including the advanced cardiac and hypertensive patient.

In the elderly patient, operative blood-pressure drops should be prevented. When severe hypotension develops in the elderly patient, even for a short period, permanent damage is done to the vascular system in almost 50 per cent of cases.

This analysis has elicited nothing which would aid detection of patients likely to develop the above hypotensive and postoperative circulatory disturbances.

Case Reports

AGENESIS OF THE RIGHT LUNG

Report of Three Cases

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UNILATERAL agenesis of the lung is relatively rare although in recent years the condition has been diagnosed more often. Still more unusual is the occurrence of agenesis with death due to aspiration of a foreign body. Having had a patient in whom this occurred and finding that no case in the literature had been completely examined with respect to the distribution of the bronchial and vascular trees in the remaining lung, we undertook to publish this single case, but before the manuscript could be prepared two other patients with this anomaly were admitted to the University Hospitals. Accordingly, all three will be discussed in the present article.

Case 1.—A two-year-old child (Baby Boy C) was referred to our Department of Otolaryngology. The child had aspirated a kernel of corn several hours previously and was markedly dyspneic and somewhat disoriented. Expiration was prolonged and wheezy with bilateral intercostal retraction on inspiration. The thorax was symmetrical. Breath sounds were heard over the left chest, but were absent over the anterior two-thirds of the right chest. No heart sounds were heard. There were no other pertinent physical findings.

Past history revealed normal birth, growth, and development. The infant's only previous illness was bronchitis at one and one-half years of age.

Chest x-rays were taken shortly after the aspiration of the kernel of corn. These x-rays were taken at another hospital and were reported to show collapse of the right lung. One of these† is presented in Fig. 1.

A bronchoscopic examination was made immediately after admission and a kernel of corn was visualized in a bronchus leading off to the right. This was subsequently identified as the left middle bronchus (*M*, Fig. 3, *C*). The kernel of corn was dislodged from this bronchus but fell into a bronchus leading to the left: the left lower lobe bronchus (*I*, Fig. 3, *C*). At this point the child stopped breathing and further efforts to revive him were unsuccessful.

Autopsy findings of interest were confined to the thorax. Upon opening the thoracic cage, a marked displacement and rotation of the mediastinum and its structures were noted. The heart lay in the right thorax and an enlarged left lung filled the left thorax and extended anteriorly across the midline to the right (Figs. 2 and 3, *A*).

No right lung or right main stem bronchus could be found. The upper portion of the right thorax was filled by the great vessels and by a moderate-sized thymus (35 Gm.) surrounded by strands of connective tissue and a small amount of fat (Fig. 2). No pleural space

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†Secured for us by Dr. L. R. Boies.

was found on the right. The heart, the arch of the aorta and its vessels were normal except for their displaced position. The normal pulmonary artery sent branches into the left lung only. A single pulmonary vein from the left lung entered the left atrium at the mid-point of its posterior wall. The trachea was in the midline and was normal, as was the larynx. Upon opening the trachea, a kernel of corn was found in the bronchus subsequently identified as that of the left inferior lobe. No gross anomalies were found except for the agenesis of the right lung and the absence of the right pleura.

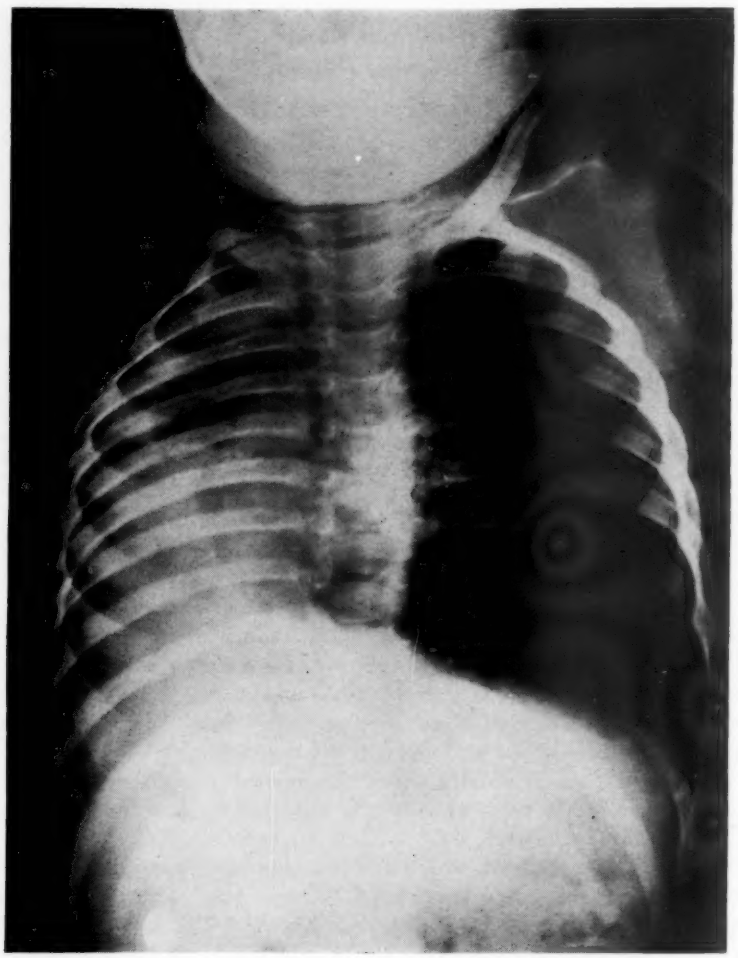


Fig. 1.—Chest plate of 2-year-old boy (Case 1) showing area covered by left pleural sac. The heart density, displaced to the right, is hardly recognizable. (For position of heart, see Fig. 2.)

Detailed anatomic dissection of the enlarged lung and sketches of it were subsequently made by one of us (E. A. B.). For some time there was doubt as to whether or not this was a left lung. At first, the nonbifurcate trachea appeared to enter an undivided mass which was flattened and bore little resemblance to a left lung. Could this not represent a reorganization of the embryonic primordium from paired anlages such as occurs, for instance, in the formation of the cyclopean eye? In partial support of this it was noted that the tracheal stem ended abruptly in a trifurcation (*I, M, S*, Fig. 3, *C*) and that superficial furrows could be developed into fissures, revealing a three-lobed organ. Furthermore, the upper of the three lobes (as determined by the apex) did not correspond in its bronchial pattern to any arrangement hitherto observed in the apical portion of the left

SURGERY
VOL. 31, NO. 3, MARCH, 1952

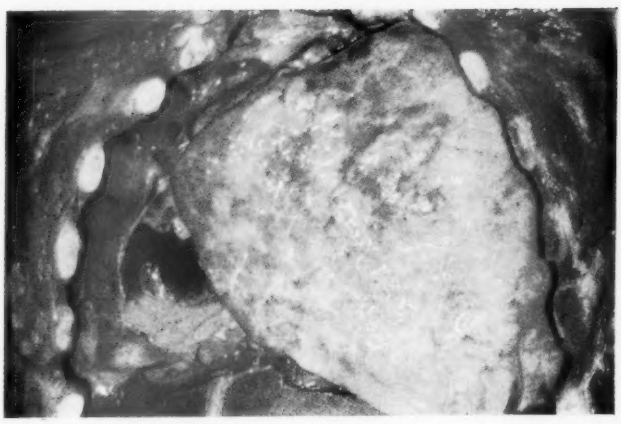
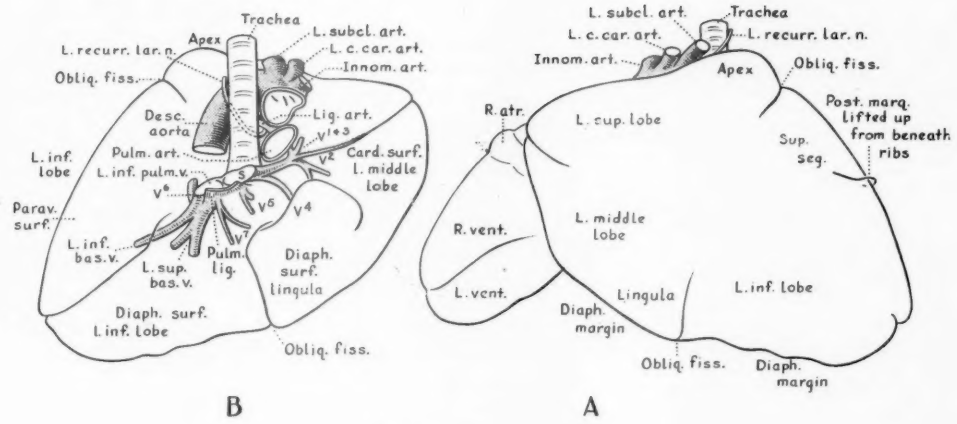


Fig. 2.—Kodachrome of chest (Case 1) as it appeared at autopsy after the sternum and costal cartilages had been removed. Note heart (bluish sheen), fat under the right costal cartilages (dark red), the thymus at the site of the removed manubrium, the liver with median falciform ligament, and the left lung flattened anteriorly, hypertrophied, and extending to the right of the midline.



Case 1

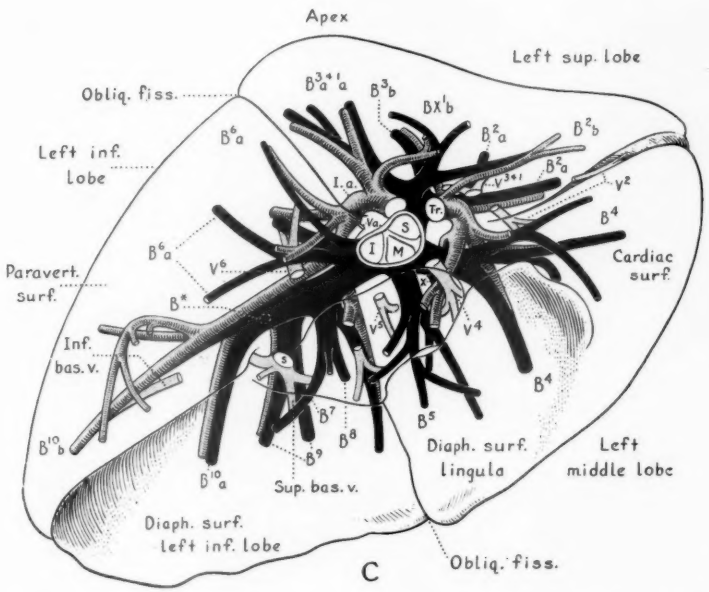


Fig. 3.—Sketches of left lung of patient in Case 1 after removal from chest (rendered for publication by Lawrence B. Benson).

A, Anterior view (cf. Fig. 2), *B*, posterior view (lung at *A* having been flopped over). This shows the three lobes and the relations of arch of aorta, left pulmonary artery (*Pulm. art.*), left pulmonary vein formed by junction of superior (*S*) and inferior pulmonary veins, and fragment of pulmonary ligament.

C, Dissection of lung—same orientation as at *B*. Note trifurcation of trachea into bronchi supplying the left superior (*S*), left middle (*M*) and left inferior (*I*) lobes, the division of the left pulmonary artery into a truncus anterior (*Tr*) and an interlobar portion (*I.a.*). The numbers indicate segmental bronchi and their primary branches (see Boyden, Dis. of Chest **15**: 657, 1949). B^1, apical bronchus; B^2, anterior; B^3, posterior; B^4, superior lingular; B^5, inferior lingular; B^6, superior bronchus; B^7, medial basal; B^8, anterior basal; B^9, lateral basal; B^{10}, posterior basal; B^* subsuperior bronchus.

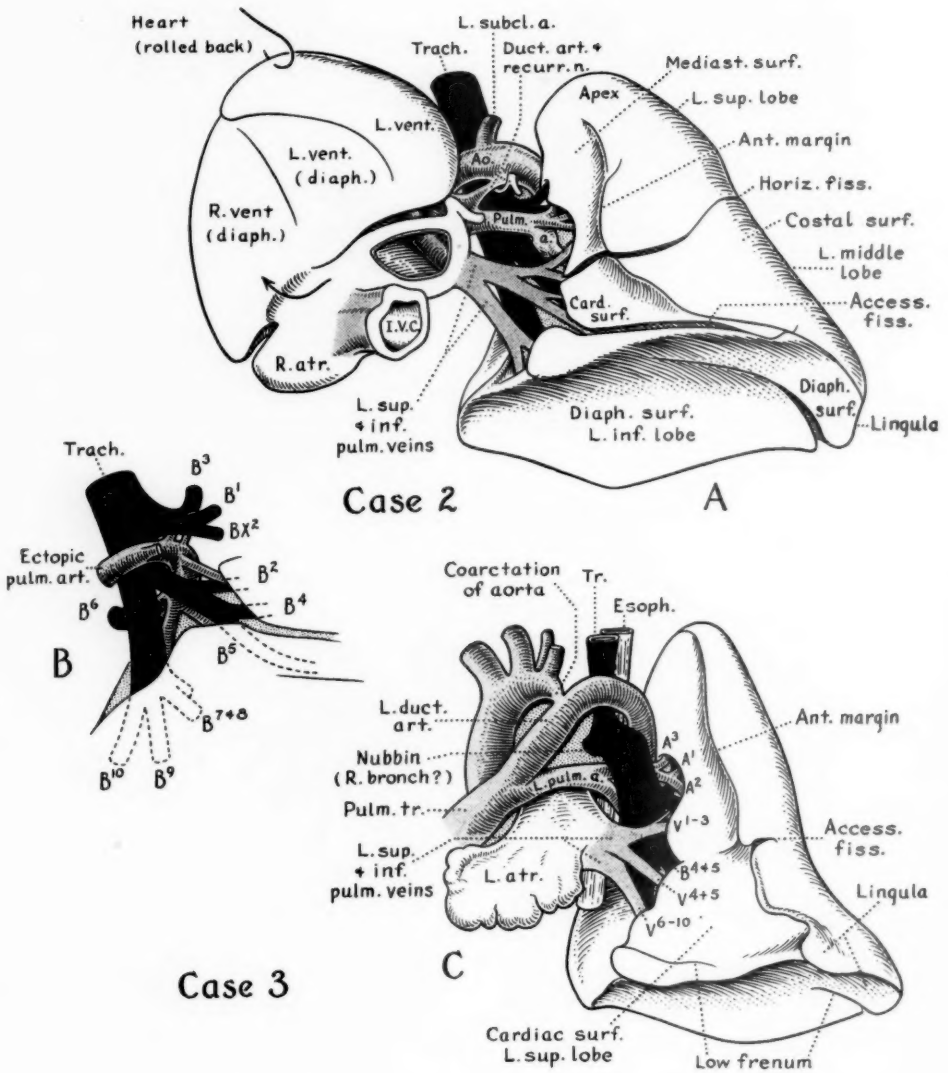


Fig. 4.—Sketches of Cases 2 and 3 (rendered for publication by Lawrence B. Benson).

A, Anterior view of three-lobed left lung of patient in Case 2, one of a pair of 3-month-old female twins. Heart has been rolled back to expose opened and dilated coronary sinus (with its appended left superior vena cava) and the course of the left pulmonary vein through the floor of the coronary sinus. The pulmonary vein enters the hidden left atrium as soon as it reaches the wall of the coronary sinus.

B, Detail of left bronchial tree and ectopic pulmonary artery in Case 2. Note that artery splits the upper lobe bronchus. (For explanation of letters B^1, B^3, etc., see Fig 3.)

C, Anterior view of left lung of patient in Case 3, a full-term male infant. Note absence of lobes, atypical position of left pulmonary artery behind the left bronchus, the nubbin on the trachea representing the right bronchus, and the enlarged ductus arteriosus accompanying coarctation of the aorta.

lung. However, the lowest lobe was found to have the pattern of a left lower lobe and then it appeared that the other two could be interpreted as the "expanded lingular type" of cleft left upper lobe described by Boyden[1] in 1949. The left middle lobe (Fig. 3, *C*) would then consist of two large segments, the bronchi of which could be identified as superior (B^4) and inferior (B^5) lingular trunks. Usually, the bronchus of such a three-lobed left lung bifurcates into a combined upper and middle lobe bronchus and a lower lobe bronchus, but in one instance (Fig. 14 of the article cited) it bifurcated into an upper lobe bronchus and a combined middle and lower lobe bronchus. Therefore one might expect, sometime, to encounter a left bronchus which trifurcated into upper, middle, and lower lobes, as in Fig. 3, *C*.

Similarly, the bizarre pattern of the upper lobe (Fig. 3, *C*) may be explained on the basis of variants found in other cleft lobes. For instance, the BX^1b arrangement is illustrated in Fig. 13 of the article cited; and the atypical union of rami of the posterior and anterior segments (B^3b and B^2b) is depicted in Fig. 15. Therefore, sometime one might expect to find a union of B^3b and B^2a, as in Fig. 3, *C*.

Further evidence that this specimen is exclusively a left lung is supplied by the arrangement of blood vessels and nerves. The single (in this case, the left) pulmonary artery (Fig. 3, *B*) is connected to the arch of the aorta by the ligamentum arteriosum (the typical arrangement). The recurrent laryngeal branch of the left vagus nerve is hooked around this ligament. The left vagus then gives off its pulmonary plexus (*Va*, Fig. 3, *C*). (No portion of the right vagus could be found in the specimen after the lung had been removed from the body.)

Just distal to the ligamentum arteriosum the pulmonary artery gives off a truncus anterior (*Tr.*, Fig. 3, *C*) which supplies the middle, and most of the upper lobe. This is not characteristic of the left side but has been observed in 16 per cent of 50 specimens (Boyden and Hartmann, 1946). The interlobar portion of the artery (*I.a.*, Fig. 3, *C*) then descends in the oblique or interlobar fissure to supply the lower lobe segments after first giving off branches to the apical-posterior segment (a typical arrangement).

Finally, the single pulmonary vein which enters the left atrium is obviously the left pulmonary (Fig. 3, *B*), since it is formed by a superior vein which drains the upper and middle lobes and an inferior vein which drains the lower lobe. Therefore, the detailed information available points to the persistence of the left lung and to agenesis of the right lung.

CASE 2.—A few months after the previously described patient came to the University Hospital, a second case of absence of the right lung was diagnosed by the roentgenologist, Dr. L. G. Rigler, and referred to us by Dr. Joseph Craig. This occurred in a 16-day-old twin baby girl (C. S.) who was hospitalized for surgical repair of a tracheoesophageal fistula. The difficult operation was unsuccessful. The left lung was excised, then dissected and drawn by one of us (E. A. B.).

The left lung was a normally shaped organ, in contrast to the somewhat flattened lung presented in Case 1. But like the preceding specimen it had three lobes (Fig. 4, *A*). The middle lobe was subdivided by an accessory fissure. Further dissection revealed that the specimen could be classified as Type IV of cleft upper lobes—the type which is characterized by the ectopic position of the left pulmonary artery (cf. Fig. 3, in Boyden[1]). As seen in Fig. 4, *B* the artery crosses the left bronchus beneath what appears to be the upper lobe bronchus instead of above it. Actually the upper lobe bronchus was split into two trunks, a superior, which supplied the apical-posterior segment (and part of the anterior), and an inferior which supplied the lingular segments and the rest of the anterior segment.

The single vein, dividing into the left upper and lower pulmonary veins appeared to enter a left atrium, but upon subsequent dissection it was found that the vein traversed the floor of a dilated coronary sinus and opened into a hidden left atrium.

CASE 3.—A third case (Baby S) appearing in this same period* was a full-term male infant who died one hour and a half after birth. Subtentorial bleeding was presumably responsible for his death, but in view of subsequent findings—coarctation of the aorta,

*Referred to us by Dr. Howard Purcell.

interatrial foramen, and absence of the right lung—it is questionable whether the infant would have survived had the bleeding not occurred. In fact he was cyanotic and took no breaths beyond a few spasmodic gasps, even though the heart action, at first, was good.

At autopsy, an unusually large amount of fat lining the right chest wall was found, but no right pleural cavity. The mediastinum was slightly displaced to the right.

Of special interest was the presence of two other anomalies—a supernumerary digit at the base of the left thumb and a constriction of the right ureter 2 cm. below the ureteropelvic junction. This had caused a moderate hydronephrosis.

Dissection of the left lung (by E. A. B.) revealed a small nubbin on the trachea, at the site of the usual bifurcation (Fig. 4, *C*), which probably represents a vestige of the right bronchus. Curiously enough, the left bronchus showed much the same mode of division as that of Case 2, i.e., the upper division (apical-posterior-anterior trunk) branched first, then the lingular trunk or lower division, but this time the left pulmonary artery passed posterior to the left bronchus—a most unusual arrangement. The lung itself was partially divided into upper and lower lobes by an oblique fissure which was defective in its middle portion.

DISCUSSION

The occurrence of three cases within a few months raises the question as to whether this condition may not be less rare than has been supposed. Yet, as recently as 1946, Smart[14] was able to collect only 104 reported cases of congenital agenesis or hypoplasia of the lung, and of these, he felt that only 75 had been correctly diagnosed, the remaining 29 cases being examples of atelectasis, pulmonary fibrosis, and other diseases. Since then some dozen additional cases have been recorded. As these add no strikingly new observations and several recent articles have reviewed the literature extensively[3, 5, 8, 9, 14] it has not seemed necessary to summarize individual cases.

The coincidence of agenesis of the lung and aspiration of a foreign body causing death is apparently exceedingly rare. Only two other cases were found in the literature. Finner's case[7] was a 22-month-old female child and Mitchell's case[11] was a 2-year-old female child. It is a further remarkable coincidence that these two cases and our case all had absence of the right lung. None of these cases were correctly diagnosed during life. Indeed, diagnosis of this condition in the living was rarely successful before the development of bronchography and bronchoscopy.

The most frequent condition with which agenesis is confused is massive atelectasis. The most important physical features of agenesis are a symmetrical thorax, equal or nearly equal respiratory movements of the chest, and marked displacement and rotation of heart and mediastinum to the affected side. In the differential diagnosis, massive atelectasis, paralysis of the diaphragm, and diaphragmatic hernia must be considered. Bronchography and bronchoscopy can demonstrate the absence of a bronchial tree on the affected side. It is remarkable that many individuals who survive the first weeks or months of life and have no other serious congenital anomalies enjoy good health and die from other causes.

As has been implied, there are different degrees of defectiveness, ranging from complete absence of one or both lungs to incomplete or abortive development of one lung. Most authors follow the classification suggested by

Schneider.[12] Group I (agenesis) consists of those cases with complete agenesis of the bronchus and lung. Group II (aplasia) consists of cases having a rudimentary bronchus with complete absence of surrounding lung tissue. Group III (hypoplasia) consists of cases having a bronchus and a variable sized hypoplastic lung. Group III would blend into the group of cases which have hypoplasia of only one or two lobes. Our three cases belong in the first group, having complete agenesis of the affected lung and bronchus, although Case 3 might possibly be included in Group II.

Such suppression of a lung must occur near the end of the first lunar month. For the lung buds first appear in human embryos in the period designated by Streeter[16] as Horizon XIII, i.e., 28 ± 1 days after ovulation. In the preceding age group (XII), 26 ± 1 days, the site is marked by a median ventral bulge of the foregut.[15]

Whether suppression in these instances was due to genetic or environmental factors could not be determined. Wilson and Warkany[18] found 5 cases of agenesis of the left lung in rat fetuses that had been subjected to a maternal vitamin A deficiency. This malformation was associated with absence of the left pulmonary artery. In a sixth fetus there was a properly developed left lung which was supplied solely through the bronchial arteries. The authors were unable to determine whether agenesis of the left pulmonary arteries was secondary to agenesis of left lungs, or the reverse. Additional defects found in vitamin A deficient rats were ocular and genitourinary anomalies (these being the most frequent) and cardiovascular anomalies, including malformations, absence and asymmetrical development of aortic arches, interventricular foramina, and general retardation of myocardial development. Altogether, 75 per cent of the offspring exhibited some degree of malformation. Recent literature has also indicated that certain other types of anomalies result from maternal diets deficient in vitamin B_2.

Warkany,[17] however, does not feel that there is sufficient malnutrition of this type in America to explain the anomalies appearing in our hospital patients. What he has shown by these experiments is that environmental changes affecting the embryo can bring about types of congenital anomalies which have been known to be hereditary in other instances; and to postulate that the same nutritional deficiency of the fetus that was caused by a dietary deficiency in the mother may be reproduced by diseases of the placenta, or by infectious agents (such as rubella) that modify the vascular supply and thus affect the chemistry of development.

A further point of interest is the mechanism of compensatory enlargement of the remaining lung. Smart[14] has shown by spirometer tests that in contrast to the enlargement following pneumonectomy, the enlargement frequently observed in congenital cases is hypertrophic and not emphysematous. This is understandable in view of Loosli and Potter's discovery[10] that in the period of formation of alveoli (6 months to term) the alveoli are carved out of the respiratory portion of the bronchial tree by the ingrowth of vascular nets (cf.

the observation of Short[13] and of Dubreuil and co-workers[4] that the lungs of premature infants can function for at least one and one-half months during the preceding canalicular period—4 to 6 months).

SUMMARY

Three patients admitted to the University Hospitals during the winter and spring of 1950-1951 were found to have agenesis of the right lung.

The first, a two-year-old boy, died during the removal of a foreign body from a bronchus. At autopsy, the somewhat flattened lung bore little superficial resemblance to a left lung, but upon dissection was found to have three lobes and could be classified as belonging to Type III of lungs having a cleft left upper lobe.

The second, one of a pair of 16-day-old female twins, was diagnosed roentgenologically but died following operation for tracheoesophageal fistula. The left lung again was three lobed, but this time belonged to Type IV—having a cleft left upper lobe associated with an ectopic left pulmonary artery.

The third, a full-term male infant, never breathed beyond emitting a few spasmodic gasps. Autopsy and dissection revealed an incompletely divided left lung, with atypical branching of the bronchial tree, a nubbin at the site of bifurcation of the trachea (which may represent a right bronchial bud), a retrobronchial left pulmonary artery, coarctation of the aorta, a supernumerary digit, and hydronephrosis due to a stricture of the ureter just below the ureteropelvic junction.

These three cases are apparently the first in which the segmental anatomy of the single remaining lung has been worked out. In each case there were striking deviations in the bronchovascular patterns of the left lung. These, together with associated congenital anomalies, suggest an interference with normal developmental processes beginning at the end of the first lunar month. Recent experiments by Wilson and Warkany show that agenesis of the lung, together with ocular, cardiovascular, and urogenital anomalies may be produced in rats by a deficiency of vitamin A in the maternal diet. In these experiments the chemistry of development has been disturbed. In man this may be accomplished hereditarily by a defective gene or environmentally by any agent that imposes upon the embryo an appropriate nutritional deficiency.

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INTRAINTESTINAL HEMORRHAGE FOLLOWING TOTAL PANCREATECTOMY FOR CARCINOMA OF THE PANCREAS

Report of a Case

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SINCE 1943, when Rockey[1] reported the first case of operative survival following total pancreatectomy (the patient succumbed after fifteen days), nineteen similar operations[2-4] have been reported. Because the operation is still comparatively rare, and because of the unique complication, the following case of intraintestinal hemorrhage following total pancreatectomy for carcinoma of the pancreas is presented.

CASE REPORT

C. E. D., a 49-year-old white man, was first seen at the Ochsner Clinic on April 27, 1950, because of increasing jaundice. Fourteen weeks before, he had had an attack of malaise with generalized pains, followed in two weeks by the onset of jaundice, pruritus, anorexia, and weakness. Meanwhile, the stools had become light-colored and foul-smelling, and were softer, bulkier, and more frequent than usual. Recently, the urine had become coffee-colored. During the illness he had lost approximately forty pounds. He had had no pain in the abdomen or back.

Physical examination revealed evidence of recent loss of considerable weight and deeply jaundiced sclerae and skin. The retinal vessels were moderately sclerosed. There were numerous scratches on the skin, particularly the extremities. The blood pressure was 140 mm. Hg systolic, and 90 mm. Hg diastolic. A soft, blowing systolic murmur was heard over the mitral and aortic areas. There was questionable elevation of the right half of the diaphragm, the abdomen was not distended, and there were no prominent superficial veins. In the right hypochondrium, a hard, slightly tender, smooth mass was palpated. It extended from immediately below the right costal cartilage to within 5 cm. of the right anterosuperior spinous process of the ilium.

Urinalysis yielded negative results except for the presence of a few uric acid crystals in the sediment. The two-hour Ehrlich test gave a result of 0.55 unit. Hemogram revealed 2.8 ml. red blood cells per cubic millimeter and 8,000 white cells per cubic millimeter. The hemoglobin was 11.5 Gm. per cubic centimeter. Differential count was not abnormal. Prothrombin time was 68 per cent of normal and the sedimentation rate was 19 mm. per hour.

Blood chemistry determinations revealed essentially normal values for urea and nonprotein nitrogen, a somewhat elevated glucose level, a considerable serum protein deficit, and an elevated cholesterol value. Bilirubin studies revealed greatly elevated values. Fecal urobilinogen was 4 mg. per cent on three occasions.

Results of electrocardiography, roentgenography of the chest, and fluoroscopic examination of the upper portion of the gastrointestinal tract were interpreted as normal. The duodenal loop did not appear enlarged or deformed. Oblique roentgenograms, however, showed questionable anterior displacement of the second portion of the duodenal loop. The possibility of a lesion of the ampulla of Vater was suggested by the roentgenologist.

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On a presumptive diagnosis of carcinoma of the head of the pancreas or of the ampulla of Vater, the abdomen was explored May 1, 1950, through an upper abdominal transverse incision, which was extended vertically to the left of the ziphisternum. Nitrous oxide-ether anesthetic, with intratracheal intubation, was used. In the head of the pancreas (Fig. 1) was an extremely hard, irregular mass about the size of an orange, surrounded by indurated tissue. The whole head, however, appeared to be mobile and no evidence of extrapancreatic extension of the carcinoma was apparent. The tail and body of the pancreas were indurated and numerous small, hard nodules were palpable. The liver, though greatly enlarged, presented no gross evidence of metastasis and there were no noticeably enlarged regional lymph nodes. The gall bladder was thin-walled and distended. The common duct measured about 2.5 cm. in diameter.

Fig. 1.—Diagrammatic representation of carcinoma of head of pancreas and extent (shaded portion) of radical structural excision. *A*, Supraduodenal portion of common bile duct. *B*, Pyloric end of stomach. *C*, Ligament of Treitz.

The gastrocolic omentum was divided below the gastroepiploic vessels, and the greater curvature of the duodenum was mobilized and reflected to the left by incision of the posterior peritoneum and fascial attachments. The gastroduodenal, right gastroepiploic and pancreaticoduodenal vessels were ligated and divided. The stomach was separated from the pylorus about 4 cm. proximal to the pyloric vein, after the lower third had been freed by ligating the right gastric vessels. The common duct was traced down to the duodenum and divided at the supraduodenal portion. The pancreas was divided at the junction of the head and uncinate process just to the left of the mesenteric vessels. The head and uncinate process of the pancreas were firmly attached to the mesenteric vessels. After dissection the mass was separated almost in toto, but some malignant tissue was thought to have adhered to the walls of the mesenteric vessels and portal veins. After the pancreas had been divided through the neck, the body and tail were extirpated and the splenic artery and vein ligated. Since the tail of the pancreas was not adherent to the spleen, this organ was not removed.

After division of the duodenum at the ligament of Treitz, the duodenum, head of the pancreas with the mass, lower portion of the common bile duct, and pyloric end of the stomach were removed en bloc (Fig. 1). The proximal jejunum was then mobilized and brought to the distal end of the common duct where choledochojejunostomy was performed. At a point 12 to 15 cm. distally, gastrojejunostomy was performed. A whistle tip (No. 24) catheter

was inserted in the jejunum between the two anastomoses, passed well into the common duct, through the choledochoejejunostomy, and brought to the skin through the left portion of the wound. Before this catheter was inserted into the jejunum, the wall had been fenestrated in several places to permit a flow of bile into the intestinal lumen. Two Penrose drains, one into the pancreatic bed and one in the region of the choledochojejunostomy, were inserted and the wound was closed with interrupted cotton sutures.

Although the operation lasted six and one-half hours, the patient remained in good condition throughout. He received 2,500 c. c. of blood during the operation.

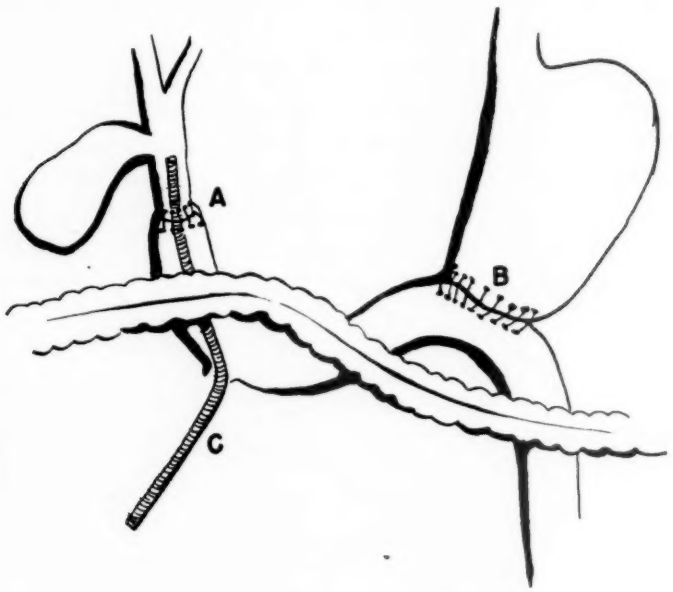

Fig. 2.—Diagrammatic representation of reconstruction of structural continuity following radical operation for carcinoma of head of pancreas. *A*, Choledochojejunostomy. *B*, Retrocolic gastrojejunostomy. *C*, Catheter drainage across choledochojejunostomy with exit through proximal jejunum to exterior of body.

Pathologic Report.—The duodenum and pancreas together weighed 120 Gm. In the head of the pancreas was a hard tumor measuring 6 by 4 by 3 cm., infiltrating the duodenal wall. It completely surrounded the distal portion of the common duct; a segment 2 cm. in length was present proximal to the lesion. The duct of Wirsung was also incorporated in, and obstructed by, this same lesion. The distal 1.5 cm. of the common duct and the sphincter of Oddi projected into the duodenal lumen; their tissues were soft and pliable. The 14 cm. of the body and tail of the pancreas which formed part of the specimen showed multiple stony-hard nodules throughout. On section, multiple areas of cystic involvement were seen but no infiltrative lesion could be identified.

Section through the tumor in the head of the pancreas revealed a moderately undifferentiated adenocarcinoma which infiltrated through the outer portion of the pancreatic substance. There was considerable fibrosis, as well as foci of necrosis, in the area of the tumor. Section through the body and tail of the organ revealed only dilated ducts, moderate inflammatory reaction, and fibrosis.

The anatomic diagnosis was adenocarcinoma of the head of the pancreas, grade III, with obstruction of the common bile duct.

Postoperative convalescence continued without incident until the afternoon of the thirteenth day, when the patient suddenly became weak and collapsed momentarily while walking to the bathroom. Although he recovered rapidly without special treatment, he continued to feel weak. Blood chemistry studies, carried out daily since operation (Table I), revealed

nothing to account for the episode. The urine showed no sugar and no ketone bodies. However, the hematocrit was only 20 per cent, with but 6 Gm. per cent hemoglobin, although four days earlier the hematocrit had been 41 per cent. Careful questioning revealed that for the previous forty-eight hours the stools had seemed darker than usual. Although there had been no symptoms or signs suggestive of ulceration, the episode was believed to be due to severe intraintestinal bleeding, probably from an acute ulcer of the gastrojejunal stoma.

Following transfusion of 4,500 c.c. of blood during the next forty-eight hours, the hematocrit rose slowly to 37 per cent. Shortly after the first transfusion the patient passed a large, tarry stool. Proctoscopic examination three days later showed no local cause for the bleeding. Five days after the hemorrhage, examination of the stools showed no blood, the hematocrit reading was 47 per cent, and examination of the upper part of the gastrointestinal tract with a barium meal revealed a well-functioning stoma with no evidence of ulceration.

When food began to be taken by mouth, the patient received insulin according to a sliding glycosuria scale and pancreatin tablets in doses of 10 gr. with each meal. Later, the dose of pancreatin was increased to 20 gr. He was also given supplementary feedings of proteinum, a high protein-vitamin mixture. Results of postoperative laboratory studies are summarized in Table I.

When the patient was discharged on the twenty-first postoperative day, his appetite was excellent and he had gained seven pounds since operation. At this time his diet consisted of approximately 200 Gm. of carbohydrate, 100 Gm. of protein, and 80 Gm. of fat daily.

Twelve weeks postoperatively, the patient had gained twelve pounds and his acquired diabetes was under satisfactory control. Eight months postoperatively, examination revealed no evidence of metastasis. The acquired diabetes was under excellent control and the patient was having one or two normal bowel movements daily. He had continued to take pancreatin, 20 gr. daily. There was no appreciable gain in weight because he had inadvertently been given a diet of 1,400 calories instead of 2,400 calories.

The patient was last seen sixteen months postoperatively, at which time there was no evidence of recurrence.

Comment.—Although palpation, inspection, and even frozen section biopsy of lesions of the pancreas characteristically may give rise to erroneous impressions, at operation in this case there was no doubt that the lesion was carcinomatous. The operative technique employed was in general the same as that described by Whipple, with reconstruction along the lines suggested by Pearse.[5] It seemed a wise precaution to provide for drainage of bile by the use of a fenestrated catheter through the choledochojejunostomy junction, with external drainage proximal to the gastrojejunostomy since the suture line was under some strain. It became evident on the thirteenth postoperative day, when the patient had a sudden, severe, painless hemorrhage, that we had, in effect, established a Mann-Williamson experiment and produced a marginal ulcer by exclusion of both alkaline pancreatic juice and sufficient bile from the stoma. The patient had had a practically full diet for the three previous days, without any significant alkalinization of the jejunum. Clamping of the catheter with limitation of oral intake to clear liquids produced prompt healing of the ulcer and gastrointestinal study with a barium meal five days later revealed no evidence of it.

This experience clearly indicates that catheter drainage should not be instituted by this technique in total pancreatectomy unless provision is made for delivery of bile close to the site of the gastrojejunostomy. Moreover, it suggests that in order to eliminate as much acid as possible from the stoma and proximal jejunum at least half of the stomach should be removed.

TABLE I. PHYSIOLOGIC STUDIES IN TOTAL

ALIMENTATION:		INTRAVENOUS					LIQUID			SOFT	
	PREOPERATIVE	POSTOPERATIVE DAYS									
		1	2	3	4	5	6	7	8	9	10
Insulin: regular		52½	52½	52½	45	45	45	30	15	20	20
PZI									5	7	7
Stools					2	2	3	1	1	1	1
Hematocrit		44		42	40	41		43		41	
Blood											
glucose (mg. %)	157	479	340	346	352	366	421	372	442	346	
urea nitrogen (mg. %)	16	30		26	31	28	31	40	27	26	
cholesterol (mg. %)	957			548	657	613			575	306	
chlorides (meq.)		107		101	102	109	102	97	107	101	
amylase (mg. %)				24						59	
CO_2 combining power (meq.)		20		23	22	29	27	19	24	20	
serum protein (Gm. %)	4.6										
albumin-globulin ratio	3.2/1.4										
Bilirubin: direct (mg. %)	11.6									10-10	
total (mg. %)	21.6									15-35	
Bromsulfalein retention (mg. %)											
Cephalin flocculation											

*Transfusion.

At no time throughout his hospitalization did the patient show any evidence of ketosis. In the absence of serum lipid studies, the cholesterol readings were taken as a relatively effective, if crude, guide to fat metabolism. The preoperative cholesterol reading of 957 mg. per cent was interpreted as an indication of an extreme disturbance of fat metabolism caused by complete blockage of pancreatic ferment. The first eight days after operation, while nourishment was being given chiefly by the intravenous route, the blood cholesterol value remained high. On the ninth day, when oral feeding was instituted and pancreatic tablets were administered, the value fell to 306 mg. per cent and remained between that level and 355 mg. per cent thereafter.

Since no metabolic and physiologic studies were carried out on the stools in this patient, the effect of pancreatin cannot be stated. It has been shown, however, that this agent causes an appreciable reduction in the bulkiness of the stools by reducing the loss of fat, nitrogen, and calories in them. Some studies show that the caloric loss has been reduced by as much as 12.5 per cent.

As has been pointed out repeatedly, total removal of the pancreas does not result in complete absence of amylase from the blood. In the case reported here, the reading of 24 mg. per cent at the time of discharge was the same as that on the third postoperative day. There is no apparent explanation for the transient rise to 59 mg. per cent on the ninth postoperative day.

Experience in the present case, like that of others,[6] indicates that postoperative management of patients after total pancreatectomy is not a serious problem today. It is somewhat difficult to stabilize the weight, though in the present case 7 pounds of the lost weight was regained while the patient was still in the hospital, and an excellent state of nutrition was maintained at all times.

Although the operative mortality for total pancreatectomy is still extremely high, it has shown a gradual reduction as the number of operations has increased. In 1948 there were only seven survivals in the seventeen cases collected by

TOTALLY PANCREATECTOMIZED PATIENT

FULL			LIQUID				FULL			
POSTOPERATIVE DAYS										
11	12	13*	14*	15*	16	17	18	19	20	21
20	30	30	20		10	30	30			
7	10	15	15	15	15	15	15	18	20	27
1	1	2	1	1	0	0	1	1	1	
		20	30	37	47	47		49		
		446		186		398			466	
		32		14		26			22	
		304		301		320			355	
		106		107					114	
									24	
		23		24		20				
3.9				5.0					5.8	
2.8/1.1				4.0/1.0						
		5.49		3-6					3.09	
		9.50		7-4					5.46	
					24					
					1+					

Gaston.[2] In the three cases reported since that time, including the present case, there were two survivals, which brings the operative mortality down to 45 per cent for the twenty cases on record. In the six cases reported by Waugh[7] from the Mayo Clinic there was only one death in the hospital.

In order to evaluate total pancreatectomy properly it is, of course, necessary to go beyond what happens in the hospital. In the fourteen recorded operations for carcinoma, exclusive of the present case, only five patients survived the period of hospitalization. There is ground, therefore, for the discussion which has arisen as to whether the procedure is ever justifiable. Some surgeons think that it is not. Gaston[2] remarked that the efficiency of total pancreatectomy in the management of malignant tumors remains to be demonstrated, and Aird[8] thought justification for the operation debatable because the survivors are "perhaps the most pathetic relics of heroic surgery."

This point of view does not seem entirely fair. As the number of successful cases increases, the impression decreases that the survivors who leave the hospital have ahead of them nothing but great suffering. Our own belief is that however little may be accomplished from the standpoint of prolongation of life, it is well worth while to try to alleviate the symptoms which arise from persistent blockage of the biliary and pancreatic ducts. Certainly it was worth while in the present case. How long this patient will survive is, of course, impossible to predict, but for the present, at least, he has been relieved of his symptoms and he is living an active and useful life. The outcome in this case, in fact, supports Whipple's point of view, that provided relief of symptoms can be assured, even though the relief is temporary, and provided the patient can resume a relatively normal mode of life, then the risk of operation becomes the lesser point to consider.

From the standpoint of principles on which neoplastic surgery should be based, total pancreatectomy is a far sounder operation than partial excision. Such operations naturally carry a higher mortality than operations for be-

nign conditions, but the outlook is improving. It is not too much to hope that total pancreatectomy may follow the course of total gastrectomy. Numerous surgeons have proved that total gastrectomy can be accomplished with a mortality rate no greater than that for partial gastrectomy; at the Lahey Clinic, for instance, a mortality as low as 8 per cent has been reported. In the light of these results, it would seem that total pancreatectomy is warranted at the present time whenever carcinoma is localized to the organ but is too extensive for partial pancreatectomy to offer any reasonable hope for cure.

SUMMARY

A case of total pancreatectomy is reported, in which an otherwise smooth convalescence was complicated by intraintestinal hemorrhage assumed to have resulted from gastrojejunal ulceration which resulted, in turn, from a relative bile-absolute pancreatic juice deficit. Measures to prevent this complication are discussed.

The decreasing mortality rate following total pancreatectomy, the easy control of the acquired diabetic state, the relief of symptoms following successful performance of the procedure, and the possibility of resuming a normal life, for however brief a time, would seem to justify the risk which the operation entails.

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Recent Advances in Surgery

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FIBROSARCOMA OF THE SOFT SOMATIC TISSUES

A Clinical and Pathologic Study

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INTRODUCTION

A MORE comprehensive knowledge of diseases of fibrous tissue has resulted from two lines of investigation. The concept that disease may affect fibrous tissue as a unit has been advanced by Paul Klemperer,[44] who catalogued such apparently diverse disease entities as lupus erythematosus, scleroderma, dermatomyositis, periarteritis nodosa, etc., under the common generic heading of "diseases of collagen," and who unified our concept of those diseases which produce abnormalities of the fibrous structural component of organs. Since certain fibrous tissue tumors are apparently under metabolic influence (desmoid tumors) increased knowledge of the reaction of fibrous tissue to metabolic, infectious, or degenerative stimuli will probably enhance our knowledge of the pathogenesis and possibly of the therapy of tumors arising from this structure. The observation that the supporting tissue of the body may be abnormally susceptible to neoplastic degeneration in certain patients is evidenced by such entities as von Recklinghausen's disease (neurofibromatosis), hereditary polyfibromatosis, and others.

Our knowledge of the natural history of tumors of fibrous tissue has been improved by the brilliant studies of Arthur Purdy Stout,[72] who painstakingly analyzed the histologic features of the numerous tumors catalogued under the heading of sarcoma, and presented criteria for a more accurate classification of these neoplasms. The in vitro technique, developed by Murray, Stout, and Pogogeff,[53] of growing tumors of the supportive structure from human hosts in culture media and noting the distinguishing differential characteristics of these tumors has contributed an important method of ascertaining the histogenesis of these various somatic tumors.

Continued investigation of the histogenesis, pathogenesis, and nosology of tumors of the soft somatic tissues will contribute data for the accurate definition of each type, an appreciation of its natural history, and a correct determination of the proper methods and end results of treatment.

This study analyzes the pathologic and clinical features of 39 fibrosarcomas of the extremities studied on the Mixed Tumor Service, the Memorial Cancer Center, New York City, from 1931 to 1948 inclusive. We believe that an analysis of a rather large series of cases observed at one institution may

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contribute to a better understanding of the neoplasm and permit an appraisal of the therapeutic modalities utilized in attempts to eradicate this type of cancer.

DEFINITION AND NOMENCLATURE

Fibrosarcoma, in this presentation, represents a malignant neoplasm which arises from fibroblasts. The identification and study of true fibrosarcomas has been difficult because the literature contains numerous examples in which the type of tissue from which the tumor arose could not be determined; many of these neoplasms were indiscriminately classified as fibrosarcomas. Paget (1865)[60] designated malignant tumors of fibrous tissue as recurrent fibroids. Cornil and Ranvier (1880)[17] reported them as fasiculated sarcomas, and Bennett (1849)[7] as fibronucleated tumors. Virchow (1864)[76] described fascial sarcomas as arising from the fascia, usually in the lower extremities, growing slowly, and resulting in cures following surgical removal. Birkett (1858)[10] and Billroth (1877)[9] recorded some of the earlier case presentations.

Although fibrosarcoma has been the subject of extensive investigation during the past century, very few definite facts have been established about this neoplasm. There exists a dearth of information to guide the surgeon in establishing criteria for therapy and prognosis. This is due to the fact that heretofore many reported lesions listed as fibrosarcomas were either benign tumors (fibromas, etc.), with the outcome exceptionally good, or contrariwise, malignant neoplasms of other types (synovial sarcomas, rhabdomyosarcomas, etc.) were erroneously reported as fibrosarcomas with the prognosis particularly poor. These histogenetic errors were made because the prototype cells of the fibroblast (mesenchyme) have multipotential capacities for development and certain neoplasms may present two or more routes of differentiation.[72] An example of this is the observation that certain synovial sarcomas will present dense fibroblastic elements throughout the section with an exceptional cuboidal-cell cleft to indicate the diagnostic characteristic of synovial origin.[56]

Fibrosarcomas may be mistaken for myxosarcomas as the result of stasis of circulation with resultant edema.[19] Foci of calcification or ossification will lull the unwary to a diagnosis of osteogenetic sarcoma.[12, 14] The perithelial arrangement which certain synovial sarcomas assume has caused them to be mistakenly diagnosed as fibrosarcomas because of the theoretical concept of a perithelial membrane of fibrous tissue structure enclosing small arterioles.[56, 81]

Much confusion has arisen pertaining to the differential diagnosis between neurogenic sarcoma and fibrosarcoma. Ewing[23] was a leading proponent of the opinion that many tumors of fibrous tissue were of nerve origin. He states, "It appears that mesoblastic cells once having been assigned to simple supportive functions have little tendency to neoplastic overgrowth. Pure fibroblasts may be drawn into a tumor process, but usually under the influence of more specialized cells, with which fibroblasts are associated, such as epithelium, endothelium, nerve structures, muscle-cells and fat-cells."[23] Adhering to this doctrine, several investigators attributed a neurogenic origin

to many spindle-celled tumors of the soft somatic tissues.[26, 64, 71, 77] Stout, however, believes that the term "neurogenic sarcoma" has little meaning and states that he has studied the essays on "neurogenic sarcoma" with faithful attention but has failed to discover what cell type or types produce this tumor, what histologic features are clearly evident by which it may be identified, or any exact or concrete information about it. He believes that many malignant fibroblastic tumors involve nerves by infiltration and may be mistakenly diagnosed as of nerve origin. He suggests that the term *neurogenic sarcoma* be deleted from all classifications of sarcomas. At the First National Cancer Congress in Memphis, Tennessee (1949),[63] it was the consensus of the Panel on Soft Tissue Tumors that Stout's point of view be accepted and the term *neurogenic sarcoma* be dropped.

Accordingly, the sarcomas of the soft somatic tissue observed on the Mixed Tumor Service at the Memorial Cancer Center were carefully reviewed, and many which had been classified previously as neurogenic sarcomas were reclassified according to new criteria, which shall be discussed in more detail under Gross Pathologic Anatomy and Microscopic Characteristics, and termed fibrosarcomas. In light of this reclassification, the analysis of these cases is pertinent and it is hoped will present the salient pathologic and clinical features of fibrosarcoma as they are recognized today.

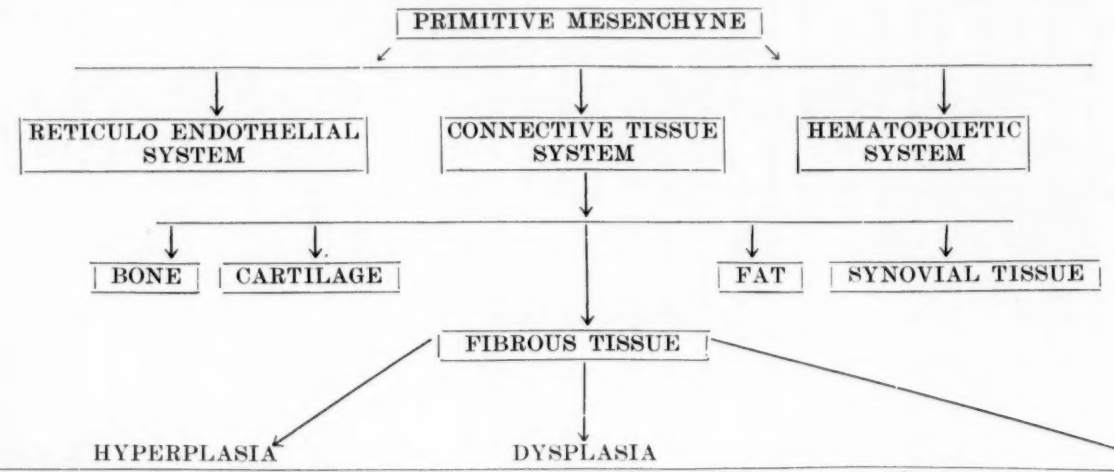
The nosology of fibrosarcoma is indicated in Table I, which presents the routes of normal differentiation of tissues from the primitive mesenchyme, and the disease entities which may develop from fibrous tissue. The chart demonstrates the close relationship of the tissues from mesenchymal origin and indicates why it is not surprising to find more than one cell type and several types of matrix (cartilage, bone, collagen, etc.) in any given sarcoma.

INCIDENCE

During the eighteen-year period from 1931 to 1948 inclusive, there have been 717 patients bearing malignant neoplasms of soft somatic tissues studied on the Mixed Tumor Service of Memorial Hospital, New York City. Among these were 39 instances of fibrosarcoma involving the soft somatic tissues. These cases represented all patients, regardless of the extent of the disease or whether definitive therapy was given or not. They included only those of the soft somatic tissues (the extremities and torso). Those of the head and neck, viscera, or other locations are not included in this report. A microscopic diagnosis was established in every instance. Accordingly, fibrosarcomas comprised 5.4 per cent of malignant neoplasms of the soft somatic tissues. Stout has studied 144 fibrosarcomas occurring in the head, neck, trunk, and extremities. Of these, 66 involved the extremities.[72]

However, it is difficult to adjudge the true incidence of fibrosarcoma from the reported series in the literature and to differentiate those which were definitely fibrosarcomas from those which were erroneously labeled fibrosarcoma because of the ambiguity of criteria in defining this particular neoplasm. The small portion of fibrosarcomas in our large series (717) of sarcomas of soft

TABLE I. THE NOSOLOGY OF DISEASES OF FIBROUS TISSUE



HYPERPLASIA

Fibrous Tissue Response to Cancer

1. Stroma of most neoplasms
2. Exaggerated
   - (a) Scirrhous carcinoma (breast)
   - (b) Linitis plastica (stomach)
   - (c) Hodgkin's disease

Myositis ossificans ←

1. Granulation tissue
2. Keloid
3. Palmar & plantar fibromatoses (Dupuytren's contracture)
4. Penile fibromatoses (Peyronie's disease)
5. Fibromatosis coli (congenital wryneck)
6. Progressive fibromyositis (hereditary polyfibromatoses—Meyenburg's disease)
7. Irradiation fibromatoses

DYSPLASIA

1. Cutis hyperplastica (Ehlers-Danlos syndrome)
2. Scleroderma
3. Rheumatic fever & rheumatoid arthritis
4. Polyarteritis
5. Lupus erythematosus
6. Dermatomyositis
7. Cushing's disease (Producing defects in fibrous tissue)

Susceptibility to Neoplastic Formations

NEOPLASIA

Benign

1. Fibroma
   - (a) pedunculated
   - (b) infiltrative
2. Desmoid tumors (desmoma)
3. Fibrous tissue and other elements
   - (a) Juvenile nasopharyngeal angiofibroma
   - (b) Fibromyoma of uterus

Malignant Fibrosarcoma

- (A) Dermatofibrosarcoma (Hoffman)
- (B) Regional fibrosarcoma
  - (a) Soft somatic tissues
  - (b) Alimentary tract
  - (c) Breast
  - (d) Periosteum
  - (e) Brain
  - (f) Genito-urinary system kidney, tunica vaginalis, penis
  - (g) Lung
  - (h) Pleura
  - (i) Mediastinum
  - (j) Trachea
  - (k) Nasopharynx and others

Mixed Neoplasms

- (A) Ectodermal and mesodermal elements
  - (a) Carcinosarcoma of uterus
  - (b) Cystosarcoma phyllodes of breast
  - (c) Sarcoma botryoides of uterus and vagina
  - (d) Wilms' embryonal adenosarcoma of kidney
- (B) Fibrosarcomatous elements almost always present with other neoplasms of mesodermal origin.

Ex: Synovioma
Rhabdomyosarcoma
Liposarcoma
Malignant neurilemmoma

somatic tissues can be explained by the fact that 261 or 36.4 per cent of our sarcomas were of undetermined histogenesis. This is an undesirable category, serving as a depository for malignant soft tissue tumors which lack sufficient histologic criteria to permit classification in some one histogenetic group. It is our belief that in any large series of soft-part sarcomas an appreciable number of these sarcomas of undetermined histogenesis must exist, as they do in this series, benefited though we have been by the studies of such competent tumor pathologists as James Ewing, Fred W. Stewart, and Frank Foot. In reports from other institutions these unclassified sarcomas have been added to the fibrosarcomas, perhaps because of their large component of fibrous tissue elements. The fibrosarcomas reported in this communication therefore, are a select group with indisputable diagnosis, and similarity of structure and behavior. The sarcomas of undetermined histogenesis, admittedly more malignant than the true fibrosarcomas, were treated with a 41.4 per cent definitive five-year cure rate.

ETIOLOGICAL FACTORS

Fibrosarcomas usually develop spontaneously with no apparent relationship to any etiological agent. In some instances fibrosarcomas apparently may develop upon damaged tissues. A better understanding of this genesis could possibly contribute to their prevention.

The Role of Trauma.—The vast study by Melzner[48] of the incidence of sarcoma which developed in patients suffering wounds during World War I, indicated how infrequent the relationship was, although it did occur. The reports of fibrosarcoma occurring in damaged tissues are recorded in sufficient numbers to indicate a definite relationship. They have been recorded as developing in war wounds,[75] operative scars,[33] and at the site of a kick by a calf.[42]

It must be emphasized that before an etiological relationship can be claimed for trauma the following postulates must be fulfilled.[22]

1. Authentic trauma.
2. Trauma of sufficient severity. (Uncertain value inasmuch as a quantitative factor is unproved.)
3. Previous integrity of the parts.
4. Region of the injury must correspond with the site of the tumor growth.
5. The date of appearance of the tumor must be consistent with the date of injury.
6. A definite diagnosis of malignant neoplasia must be established.

Meyerding and co-workers[50] found a relationship to exist between trauma and the development of fibrosarcoma in 11.2 per cent of their 152 patients, although Ivins and co-workers,[42] who analyzed the material at the Mayo Clinic at a later date, could establish a definite relationship between trauma and

the formation of fibrosarcoma in only one patient. In no instance of our series could trauma be considered as the sole etiological agent in the formation of fibrosarcomas, although a number of patients did complain of injury preceding the discovery of the tumor mass.

Fibrosarcomas occur in scar or granulation tissues. Ewing[23] called attention to this entity and titled this lesion "granulation tissue sarcoma." He thought that infection was usually present and that the grade of malignancy varied between wide limits. Stout[72] states that in thirty-six patients of his series the neoplasm developed in scar tissue or the site of previous injury. Fibrosarcomas have been reported to have occurred at the site of burn,[25] chronic varicose ulcers,[31] and at the site of arsenic injection.[35] The following case reports illustrate this mode of origin of fibrosarcoma developing in scars.

Fig. 1.—Origin of a fibrosarcoma in a burn scar.

CASE 1, FIBROSARCOMA DEVELOPING IN BURN SCAR.—G. Y., a 53-year-old blacksmith, applied on June 18, 1943, with the chief complaint of an ulcer developing in the middle of a huge burn scar situated on his back.

When he was 6 years old, his clothing had caught on fire and he had sustained a severe burn which required approximately 4 years to heal under medical treatment but without skin grafting. More than 30 years later, an ulcer developed in the center of the renitent scar; this ulcer gradually increased in size for a period of 6½ years until the date of admission. It was widely excised and a plastic repair of the defect was accomplished. The pathologic report was basal-cell epithelioma. The significant feature of the history was that the scar was approximately 35 years old when it began to degenerate.

He remained relatively free of discomfort until January, 1951, at which time a new tumefaction began in another portion of the scar; this grew rapidly and the tumor fungated out through the skin to form a firm, vascular, infiltrating, and ill-defined mass measuring approximately 5 by 7 cm. in diameter. The biopsy revealed sarcoma. A huge rectangle of

skin was removed down to and including the superficial muscles of the back. Lateral skin flaps were elevated and mobilized by sliding, to cover the defect in its entirety. Our pathologist reported the tumor to be a fibrosarcoma. It was definitely different from the metaplastic spindle-cell carcinoma which occasionally occurs in scars, notably scars after x-ray burns (Fig. 1).

CASE 2, DEVELOPMENT OF FIBROSARCOMA IN LAPAROTOMY SCAR.—Mrs. A. McK., a 55-year-old woman, had a carcinoma involving the transverse colon, which was surgically excised together with a segment of jejunum which was incorporated with the carcinoma. Anastomosis of colon to colon and jejunum to jejunum was performed. The excised tumor was an adenocarcinoma of colonic origin. The date of the operation was February, 1943. Two years later a lump appeared in the center of the operative scar. A second excision was performed in February, 1945. This lesion was an intramural tumor not involving viscera and required removal of only a segment of the abdominal wall. On examination of the excised specimen* it was pronounced to be a fully malignant spindle- and giant-cell sarcoma.

Postoperative high voltage x-ray therapy was administered. There has been no evidence of recurrence 5 years after the operation for sarcoma of the abdominal wall, and 7 years subsequent to the colectomy for carcinoma.

The Role of Irradiation in the Formation of Fibrosarcomas.—There are a number of recorded instances wherein fibrosarcomas developed in tissues which were heavily irradiated.[38, 55, 61, 79, 80] Irradiation produces a dense avascular hyalinization. Elastic fibers apparently disappear and the overlying skin, which is atrophic, often breaks down and becomes infected, rendering the site of irradiation favorable for malignant degeneration. An interesting review of radiation injuries with the development of malignant neoplasm by Teloh, Mason, and Wheelock,[74] stressed the sad commentary that in the majority of patients in whom neoplasms developed following radiation treatments, the irradiation was given for such benign lesions as psoriasis, keratoses, warts, and others. Stout[72] cites 4 cases of fibrosarcoma developing upon irradiation fibromatosis and calls attention to the fact that 2 such patients were treated for hypertrichosis, one for psoriasis, and one for an undetermined skin lesion on the dorsum penis. Epidermoid carcinomas developing in irradiated skin commonly exhibit spindle-cell metaplasia to such a degree that the tumors have been confused with sarcomas.

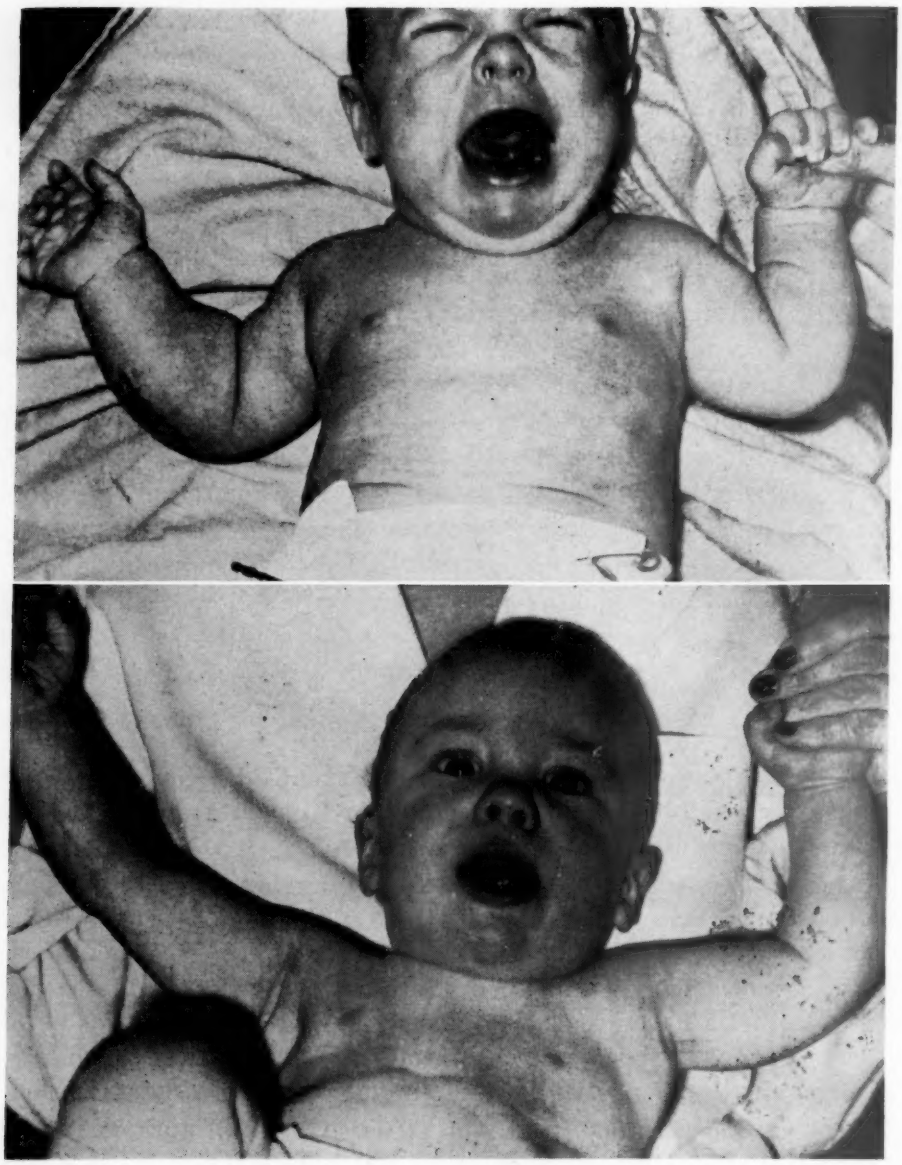
Congenital Relationship.—A congenital relationship is suggested in Case 31, where the sarcoma was noted in the patient at the age of 6 weeks. This was the only such instance (Figs. 2 and 3). We have had 2 congenital rhabdomyosarcomas and 1 congenital liposarcoma all occurring on the extremities. Hudson describes a fibrosarcoma developing in utero.[41] There was nothing in these data or in the reports of the literature indicating any hereditary relationship, yet the desmoplastic diathesis in general tends to be a familial trait.

Malignant Degeneration of Benign Tumors.—Several authors have traced the transition of fibrosarcoma from simple fibromas.[24, 25, 30, 37, 78] However, it is impossible clinically to distinguish fibromas from slowly growing fibrosarcomas. The natural history of fibrosarcomas as revealed in this study indicates the

*By Dr. Frank Foot.

low-grade malignancy and insidiousness of growth before they produce symptoms of sufficient degree to cause the patient to seek medical attention. Unencapsulated fibromas of fascia, especially of the extremities, may be classified on excision as histologically benign, but are prone to recur, to infiltrate, to extend centripetally toward the trunk, and to show increasing cellularity with successive recurrences.

A.



B.

Fig. 2.—*A*, Fibrosarcoma involving the right forearm in a 2-month-old infant. Scar represents site of biopsy which revealed fibrosarcoma, Grade III. (Patient of Dargeon, Coley, and Higinbotham). *B*, The same patient 7 months after a course of x-ray therapy with complete shrinkage of tumor.

Miscellaneous.—Fibrosarcomas in a bone lesion of osteitis fibrosa cystica secondary to a parathyroid adenoma have been described.[37] No etiological relationship was observed between the occurrence of the sarcoma and occupation, race, and nationality of the patient. No metabolic abnormalities were observed and blood chemical studies, when performed were normal in all instances.

We have reported the development of sarcoma in myositis ossificans and an unusual instance of fibrosarcoma occurring in myositis fibrosa progressiva (Meyenburg's hereditary polyfibromatosis) which caused death by pulmonary metastasis.[57]

A.

B.

Fig. 3.—*A*, Roentgenogram demonstrating invasion of ulnar bone by fibrosarcoma. (Same patient as Figure 9.) *B*, Posteroan.erior roentgenogram demonstrating repair of osseous defect 3 years after x-ray therapy. Patient is alive and free of disease 5 years after x-ray therapy with slight shortening of right forearm but complete function.

AGE AND SEX DISTRIBUTION

Sex.—There is a preponderance of women in this series. Twenty-four of the patients were women and fifteen men. Others have described a predilection of fibrosarcoma for the male sex,[50, 78] although Heller and Sieber find a slightly higher incidence in women.[37]

Age.—Fibrosarcoma is essentially a disease of younger adults. The average age of this group was 39.4 years. Fifty-three per cent of all fibrosarcomas in this series occurred in patients between the ages of 30 and 50 years with the

incidence gradually and equally tapering off on either side into the younger and older age brackets. The youngest patient was 6 weeks old when the tumor was noted, and the oldest was 70 years of age (Table II). There was no significant difference between the ages of the men who averaged 38.3 years and the women whose average age was 40 years. The average age of this group is similar to that of patients bearing synovial sarcoma (average age, 36.3 years) and those having dermatofibrosarcoma (average age, 44.3 years).

Reports in the literature indicate a somewhat higher age but this is probably due to the fact that other types of sarcomas may have been included with the fibrosarcomas.[77] Stout[72] and Wilson[78] report a similar age distribution of patients with fibrosarcomas.

TABLE II. AGE* OF PATIENTS WITH FIBROSARCOMA

YEARS	0-10	11-20	21-30	31-40	41-50	51-60	61-70	70+
Number of cases	4	2	2	12	8	6	5	0
Per cent of cases	12.5	5.1	5.1	30.8	20.5	15.4	12.8	0

*Age on admission to the Memorial Hospital.

LOCATION

Fibrosarcomas occur most frequently on the extremities, and the majority of cases in this report are of the extremities with the exception of 7 which were present on the torso (Table III, Fig. 1). Fibrosarcomas may occur anywhere in the body where fibrous tissue is present, and have been described within the alimentary tract,[18, 20, 28, 29] mesentery,[47, 65, 72] omentum,[45, 52, 66] retroperitoneal region,[40, 46, 77] liver,[34, 70] breast,[1, 27, 39, 69] central nervous system,[5, 68] kidney,[6, 51, 62] urethra,[3] vagina,[77] lung,[4, 43] mediastinum,[21, 67] upper respiratory tract including the lip, tongue, trachea, larynx, nasopharynx, nasal cavity, orbit, and lower eyelid, etc.[72]

TABLE III. LOCATION OF THIRTY-NINE FIBROSARCOMAS

ANATOMIC SITE	NUMBER OF CASES	PER CENT OF TOTAL
Upper extremity	22	56.4
Shoulder	10	25.6
Arm	3	7.7
Elbow region	5	12.8
Wrist	1	2.5
Hand	3	7.7
Lower extremity	10	25.6
Thigh	6	15.4
Knee region	2	5.1
Foot	2	5.1
Back	4	10.2
Chest wall	2	5.1
Abdominal wall	1	2.5

In Stout's[72] series of 218 fibrosarcomas observed in the Laboratory of Surgical Pathology, Columbia University, between 1907 and 1946, 58 occurred subcutaneously and 37 within the muscle, tendon, or tendon sheath. Thirty-six were noted within scars and 29 were in the skin. Next in frequency were those

of the abdominal musculature in which he observed 12, and 12 also in the periosteum. Meyerding and co-workers,[50] had observed about 184 fibrosarcomas of the extremities. The lower extremities were involved most frequently, namely, in two-thirds of the cases. It is not surprising that the feet and legs were more frequently involved than the upper extremity because of the greater bulk of fibrous tissue contained within the lower extremity.

Yet in our series the upper extremity was most frequently involved, being the site of fibrosarcoma in 22 instances (56.4 per cent) (Fig. 4). The lower extremity was invaded in 10 instances (25.6 per cent), and the torso (chest, back, and abdominal wall) in 7 instances. The shoulder region was the most frequent location for the origin of fibrosarcoma (15.4 per cent) in the series reported here. The thigh was next in frequency, being involved in 6 cases (15.4 per cent) (Table III). The hands and feet were rarely involved

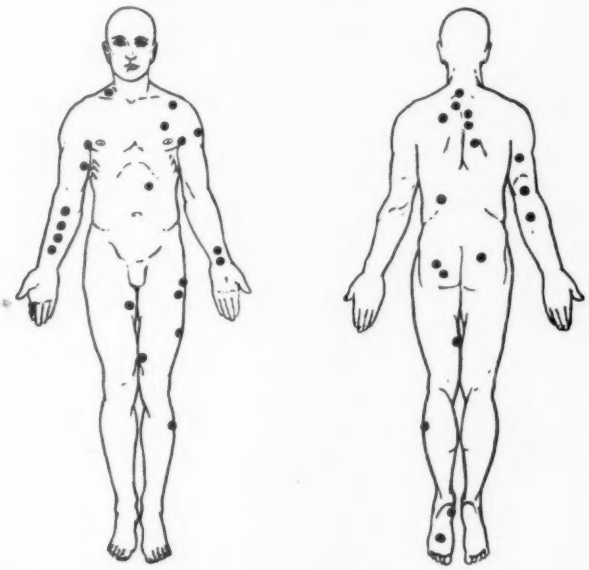


Fig. 4.—Scattergram to illustrate the regional distribution of fibrosarcoma. Observe the predilection for the shoulder and thigh.

by fibrosarcoma. Fibrosarcomas are seldom located about joints. The abdominal wall is a common site of fibrous tissue tumors (desmoid tumors). This interesting neoplastic entity which occurs most frequently in women and is often related to pregnancy has been discussed in another paper of this series and is not included in this review.[11, 58] Fibrosarcoma, exclusive of desmoma, has been observed to arise in the abdominal wall only once at this hospital. Stout has observed fibrosarcomatous involvement of the abdominal wall (excluding desmoid tumor) in 13 instances in his series of 144 fibrosarcomas of the soft parts.

SYMPTOMATOLOGY OF FIBROSARCOMA

Fibrosarcomas unfortunately do not present a characteristic symptom complex which could serve to differentiate this malignant neoplasm from benign tumors or from other malignant tumors which involve the soft somatic

tissues. The most frequent symptom is the presence of a painless mass which starts insidiously, grows slowly, and either reaches huge proportions or, more rarely, causes the patient to seek treatment because of pressure against a nerve which produces pain or other disability. The tumor may occasionally present itself as a painful mass. Least frequently, the onset of pain with no mass, or followed in a variable time by the presence of a tumor may be the sequence of events. In this series 33 patients (84.6 per cent) presented as the initial symptom, the presence of a painless mass. In 3 patients, the initial symptom was a painful mass, and in 3 other patients, the neoplasm was heralded by the presence of pain with no mass. The average delay from onset of the first symptom until establishment of the diagnosis was 32.7 months, a long delay, indeed, in the treatment of a malignant neoplasm.

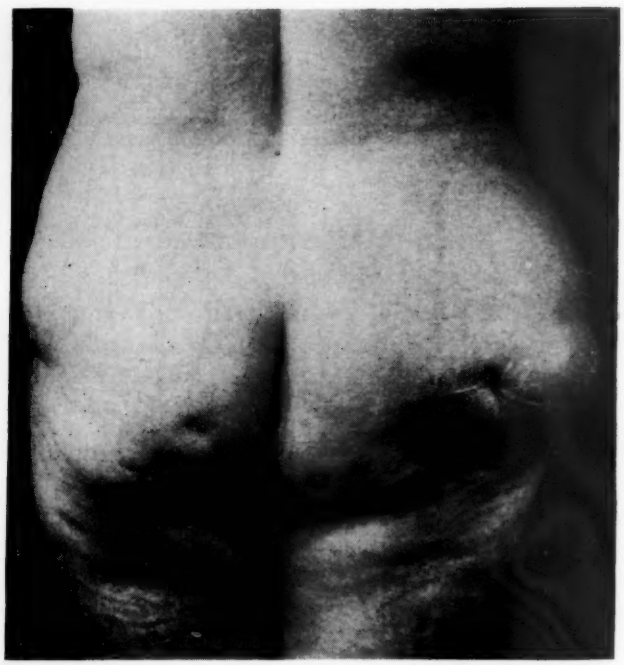


Fig. 5.—Fibrosarcoma of right buttock which had been locally excised 2½ years before. This patient developed pulmonary metastases and succumbed six months after wide local excision.

Painless Mass.—The fact that the tumors usually arise from subcutaneous aponeuroses, or muscle covering, makes it understandable why they would begin as painless subcutaneous masses which would not produce pressure symptoms for a considerable time. The insidious onset and prolonged growth is characteristic of fibrosarcomas (Figs. 6 and 7). When first observed at this institution, the tumors usually averaged between 4 and 7 cm. in diameter. They were not well delineated but seemed to blend gradually into the surrounding tissue. They were not freely movable but the overlying skin could be moved with ease over the tumor (a point of distinction from the closely related dermatofibrosarcoma protuberans).[59] The benignity of the clinical

course usually results in undue delay before the patient presents himself for treatment. Thus, of the 33 patients in whom the initial complaint was the presence of a painless mass, the average delay from onset of the symptom until the institution of adequate treatment was 2.4 years.

Fig. 6.—Massive fibrosarcoma in the thigh of a 65-year-old woman. Status after two unsuccessful attempts at local excision before admission.

Fig. 7.—Fibrosarcoma involving the right elbow region. There had been unsuccessful attempt at local excision and postoperative x-ray treatment elsewhere two months previously. The patient was free of sarcoma four years after wide local dissection.

The growth characteristics of fibrosarcomas follow one of three patterns:

1. They usually grow slowly from their inception until they reach a relatively large size.
2. They appear to remain stationary for many years before rapid growth occurs.
3. They may grow very rapidly and metastasize early.

Examples of the slow growth is indicated in 2 patients who delayed 120 to 180 months respectively while the tumor grew slowly. Three other patients each delayed 36 months while the tumor gradually increased in size. Contrary to the previously described benign clinical course was that of one patient, whose tumor was present but 4 months before treatment and who died 2 months after therapeutic attempts. Another patient also had a highly malignant fibrosarcoma; her tumor was known to be present for one month before admission and she died one month later. In no cases in this series did the tumor exist as an apparently benign, harmless neoplasm for a prolonged time and then suddenly begin to grow rapidly.[78]

The following case report presents a fascial fibrosarcoma with continuous growth over a period of 21 years without metastases.

CASE 3, FIBROSARCOMA OF UPPER EXTREMITY: TWENTY-ONE YEARS' DURATION.—L. B., a 30-year-old woman, the mother of nine children, injured the back of her left hand in March, 1928, following which a small lump, about 1 cm. in diameter appeared. Six months later similar nodules appeared over the lateral aspect of the left upper arm. About a year later the lump on the upper arm was 10 cm. in diameter and the lump on the back of the hand 6 cm. in diameter. From this date until seen by one of us in April, 1934, five different operative procedures, namely local excisions, were performed. At this time the left arm was markedly edematous, atrophic, and practically useless, with only slight flexion of the fingers and elbow. The tumor had extended from the dorsum of the hand up the entire arm to involve the entire circumference of the upper arm, the left infraclavicular region, the left axilla, the left scapular region, and the left supraclavicular space. A review of the submitted microscopic slides revealed a fascial fibrosarcoma of low-grade malignancy. An interscalpulothoracic amputation was refused. Palliative high voltage x-ray therapy was given at different times during the succeeding ten years with good growth restraint and slow, progressive diminution in size of the tumors irradiated.

The regression became so complete and paresis so improved that three years later the patient was able completely to flex the arm at the elbow. In September, 1938, the atrophy of the shoulder girdle, anteriorly and posteriorly, had been very great, but the tumor process was inactive in this location. It had extended, however, into the neck where it infiltrated over the isthmus of the thyroid and posteriorly as far as the spinal column to which the tumor was adherent causing marked torticollis. At this time some difficulty in swallowing was experienced due to pressure on the cervical and upper thoracic esophagus. By November, 1938, fluoroscopic and x-ray studies showed the tumor to be extending by direct invasion intercostally into the chest where it was producing a bulky tumor within the upper left pleural cavity. There was apparently no invasion of the lung, but direct growth of the tumor within the chest and continuity with the neoplasm in the region of the shoulder girdle. The left first rib was largely destroyed through pressure. There was a paralysis of the left phrenic nerve with marked elevation of the left leaf of the diaphragm.

At various times within the next 2 years individual recurrences developed throughout the entire upper extremity and these were controlled satisfactorily by x-ray therapy, and in some instances by palliative surgery or local excision.

In August, 1940, the patient experienced inability to swallow even liquids and a Janeway gastrostomy was performed for feeding purposes; it has been used continuously by the patient for the past nine years. Her weight had come down from 172 to 92 pounds, but after the gastrostomy feedings she maintained her weight. In 1941, evidence of partial destruction of the left humerus was observed with evidences of bone regeneration following x-ray therapy. Three pathologic fractures occurred in the left humerus between 1941 and 1949. Eventually complete paralysis of the extremity occurred and in May, 1949, a disarticulation of the humerus from the glenoid fossa was performed. There was no possibility of removing the tumor in its entirety because of its extension within the chest and its tendency to encircle the left upper neck semicircumferentially. At no time was there distant dissemination of this cancer.

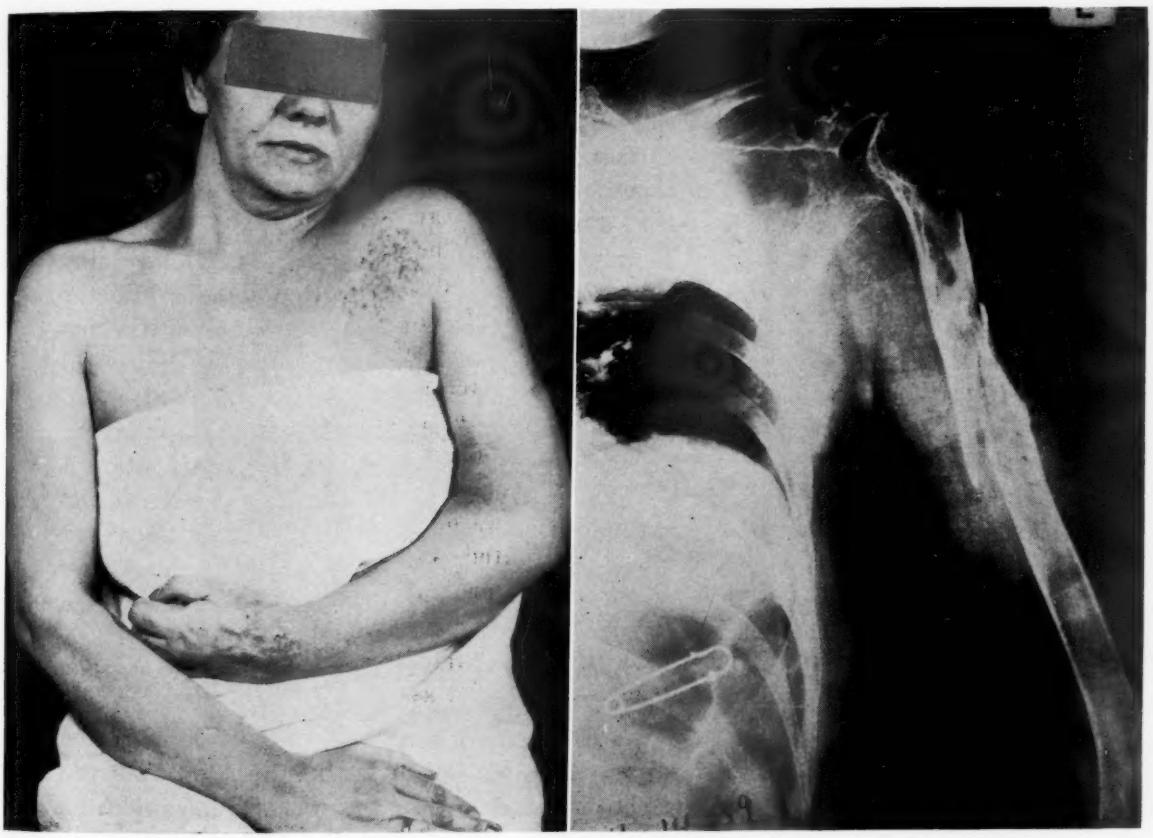


Fig. 8.—Clinical photograph and roentgenogram of a patient with fibrosarcoma which involved a large portion of the left arm, invaded bone, produced a pathological fracture, and infiltrated the chest, compressing the esophagus and requiring gastrostomy. Duration of course—21 years.

Pathologic Report.—At least 20 specimens have been available for microscopic study and all of them revealed a fascial fibrosarcoma of low-grade malignancy. It is considered to be a nonmetastasizing type, but one that would tend to recur locally. The lesion was never encapsulated. The diagnosis, on careful study of the disarticulated arm, was confirmed. The calcified sections of the bone showed no direct invasion of the bone by the tumor.

The course of the disease is typical. This patient is living 21 years after the known onset of the fascial sarcoma on the dorsum of the hand and 15 years after application for treatment. The process has been one of diffuse infiltrative, centripetal extension of the tumor from the hand up to and within the thoracic cavity in continuity.

Painful and Tender Mass.—It is of interest that the 3 patients who complained of a painful, tender mass presented themselves for treatment relatively early, averaging 3.8 months after the onset of their symptoms. One patient observed a swelling of the right elbow, with numbness and paralysis of the right thumb as a result of pressure against a nerve. Another patient detected a painful mass present in the right scapular region and another complained of a painful mass in the inner aspect of the left thigh which presented itself 4 months after trauma to this region. The patient who complained of a swelling of the right elbow and numbness of the thumb, was given antisyphilitic therapy by her local medical doctor for this symptom, without benefit of a Wassermann test, which resulted in a delay of 3 months before the true diagnosis was established and adequate treatment instituted.

Pain With No Mass.—Pain without a mass was the chief complaint of 3 patients and these patients also sought immediate medical attention an average of 4 months after the onset of their symptoms. One patient whose initial symptom was pain which had been present for a period of 7 months before admission without the presence of a mass, revealed a periosteal fibrosarcoma of the left femur for which a hemipelvectomy was performed. A long delay ensued in the establishment of the diagnosis because her local medical doctor diagnosed arthritis for which he gave intravenous injections. Since the patient was not relieved she went to another local physician who also diagnosed arthritis and gave her more intravenous therapy. Another patient also had pain in the medial aspect of the right side without the presence of a mass for a period of 4 months, after which the mass presented itself at this site. A local medical doctor in this instance referred the patient to the Memorial Cancer Center but the patient did not present himself for a period of 1½ years, and when he did come, he refused therapy. This patient died 1 year after our examination, 2 years and 8 months after the onset of symptoms for which no therapy whatsoever was given.

GROSS PATHOLOGIC ANATOMY

Fibrosarcomas usually originate as small, firm, painless nodules which grow slowly for a long time, and may attain a large size before being observed by the patient. They are commonly found within the muscles arising from structural septa or more frequently occur subcutaneously in association with aponeuroses. At the growing periphery of the tumor small nodularities develop sometimes beyond the palpable margins of the fibrosarcoma; these nodularities become agminated, fuse, and are ultimately incorporated in the progressive growth of the sarcoma (Fig. 5). As a rule, the tumor appears to be encapsulated and large tumors which have developed over prolonged periods usually have a thickened capsule, which is intimately attached to the tumor and cannot be separated from it. This is due to small fasciculi extending from the capsule into the tumor, and in some instances to lobulations. The capsule can usually be shelled out from its bed. However, this is most inadvisable because the tumor may have infiltrated through the capsule and extended into the contiguous structures.

The tendency of fibrosarcomas to force themselves against neighboring structures rather than infiltrate them is characteristic and produces some interesting pathologic results. When they occur within muscle groups (Fig. 9) they grow to rather bulky proportions because of the yielding nature of the muscular tissue and produce at times a secondary capsule consisting of a thin rim of muscle. When they arise from periosteum, that portion which grows into the soft tissue becomes bulky, but that portion which is forced against the bone becomes denser and the tumor may encircle portions of the bone. The response of the pressed bone varies; it usually undergoes pressure atrophy lending itself to invasion by the neoplasm (Fig. 8). Contrariwise, the bone may resist infiltration by cortical thickening and ebonization.

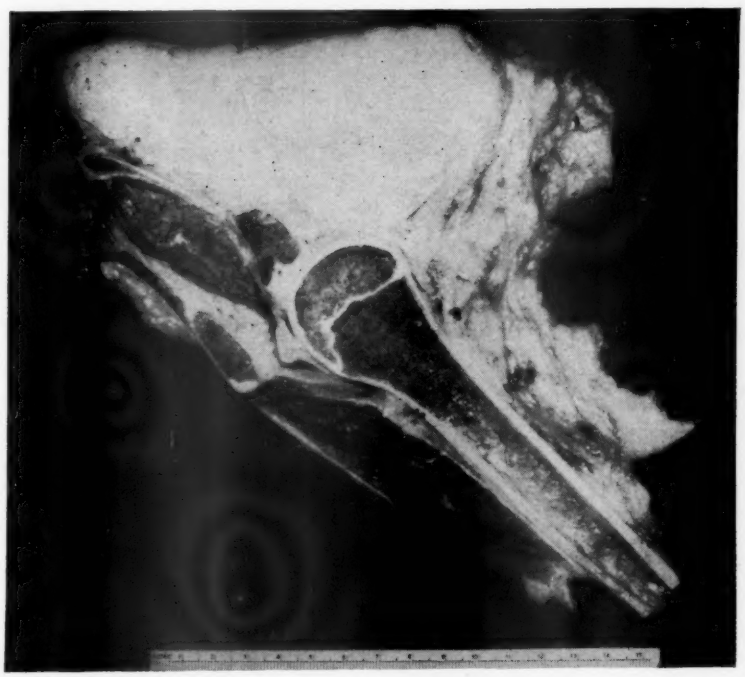


Fig. 9.—Fibrosarcoma involving the right shoulder. Patient is well 5½ years after interscapulothoracic amputation. Note how the tumor presses against but does not invade the contiguous muscle and bone.

Subcutaneous neoplasms may press against the skin, producing pressure atrophy and ulceration either spontaneously, or more frequently, following trauma (Fig. 10). The neoplasm may then fungate. This phenomenon does not usually occur, because the tumor tends to follow routes of least resistance and extend along fascial planes (Fig. 11). Ill-advised attempts at biopsy or local excision may produce the cutaneous break and the neoplasms may then fungate rapidly through the skin.

When they arise close to joints they may extend into the synovial tissues and be so intimately fused to them that it is difficult to identify the exact point of origin (Fig. 9). The tendency of the neoplasm to mold itself against structures with which it comes in contact accounts for the rather common

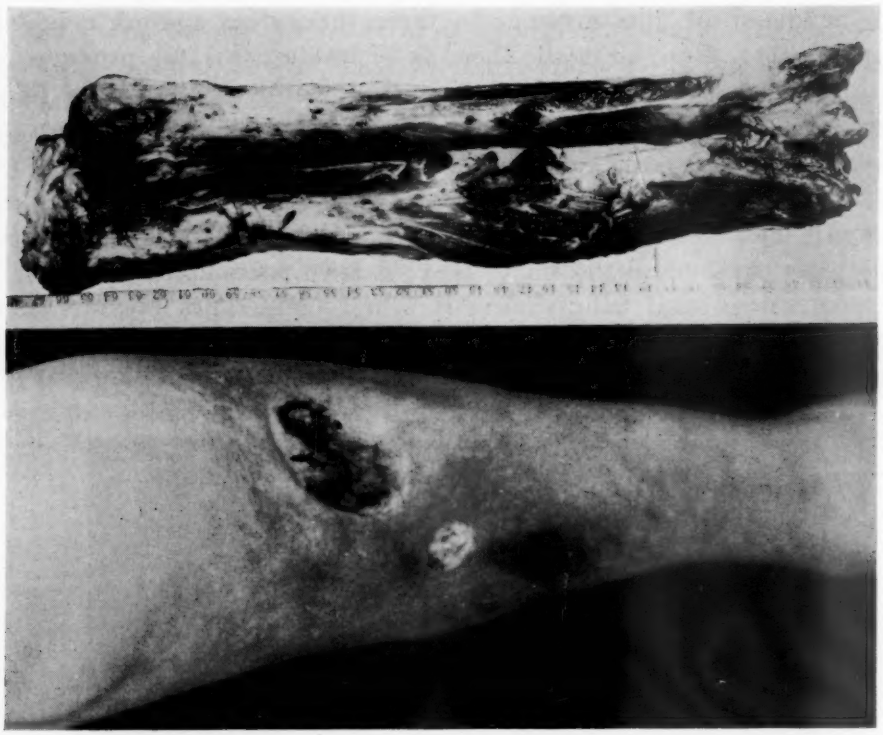


Fig. 10.—Diffuse fibrosarcoma of left leg in a 21-year-old woman; bone invasion. Metastases to the lungs occurred three months after onset.

A. *B.*

Fig. 11.—*A*, Bulky fibrosarcoma which involved the lower abdomen and produced inguinal metastases. *B*, Clinical status after surgical extirpation by wide local excision and groin dissection in continuity.

finding of a larger and smaller nerves and blood vessels traversing the tumor mass.

Because the tumor usually grows in an expansive manner (all portions of the neoplasm contributing to the growth), it is unusual to find large necrotic foci, except in the most malignant fibrosarcomas. The tumors are firm to hard in consistency and present a grayish pink color with a roughened, ropy surface. Cut section usually reveals an interlacing maze of fibrouslike strands extending in all directions and presenting a glistening, stringlike surface (Fig. 9). Scattered sporadically about may be foci of edema, necrosis (rather uncommon), smaller or larger cystlike lesions containing hemorrhagic, dirty red fluid, and regions of frank intratumoral hemorrhage. Small deposits of cartilage or bone may occasionally be observed.

MICROSCOPIC CHARACTERISTICS

Fibrosarcomas present features illustrating attempts to continue the normal functioning capacity of the cells, namely the production of collagen. Therefore variable amounts of stroma are usually present within the neoplasm. In a well-differentiated fibrosarcoma each cell is contained within a wrapping of slender argyrophilic fibrils (Fig. 13). This neoplasm simulates adult fibrous tissue in other ways. The size and shape of the cells are uniform; the nuclei are spheroid and do not stain deeply. Mitoses are not seen. The cells are in orderly arrangement and are dispersed among its abundant collagen stroma which weaves into an interdigitating pattern. An occasional blood vessel may be seen but necrosis is very rarely, if ever, observed (Fig. 12).

Along the periphery of the tumor, the structure, although identical to that of the central portions, may have a more flattened appearance, especially if the tumor is pressing against a hard structure such as bone. The cells are more elongated and the collagen fibers compressed against each other so that the individual autonomy of each strand is lost in the compressed homogenous structure. If the tumor is extending along a fascial plane this pseudocapsular arrangement is absent and the cells and collagen of the fibrosarcoma may be intermingled with the cells and stroma of the tissue being invaded (usually muscle (Fig. 14). It is to be emphasized that true fibrosarcomas seldom produce structures of other mesodermal derivatives (synovioblasts, osteoblasts, angioblasts, etc.), and if other structures are noted, especially when it is certain that the foreign structure does not represent the edge of the growing tumor mass, the neoplasm is, in all likelihood, not a pure fibrosarcoma.

From this well-differentiated, rather benign form of fibrosarcoma every degree of increased malignancy may be noted. Although fibrosarcomas usually exhibit a rather uniform degree of malignancy throughout the entire tumor, a very malignant nidus may be seen in an otherwise well-differentiated tumor.

As fibrosarcomas become more anaplastic, less and less stroma becomes evident with increased crowding of the cells. The cells tend to become smaller and hyperchromatic. They do not have a uniform size and shape. They tend

Fig. 12.

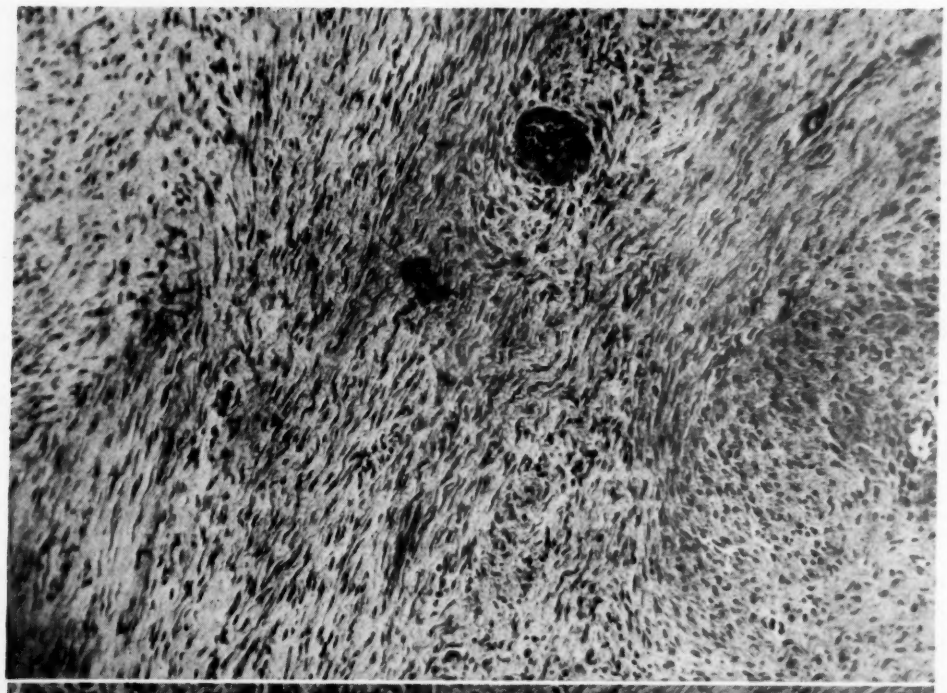


Fig. 13.

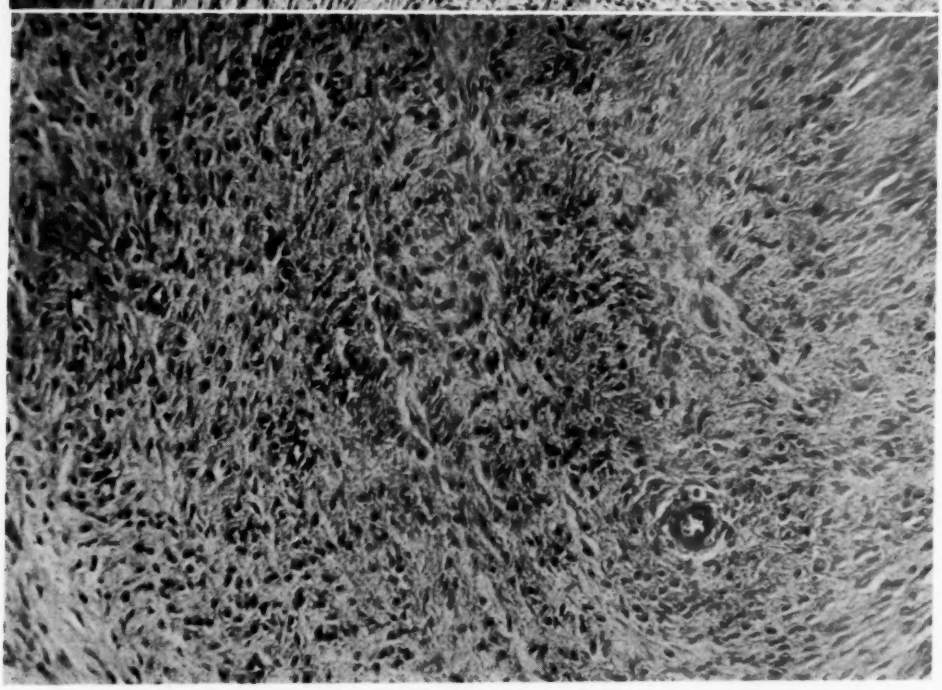


Fig. 12.—Photomicrograph of a recurring fibrosarcoma which developed in the right axilla of a 43-year-old woman. After two recurrences following local excision an interscapulothoracic amputation controlled the neoplasm and the patient was well 6 years after treatment. Note the spindle-shaped cells arranged in a somewhat regular fashion. There is an abundance of fibrous tissue stroma.

Fig. 13.—Photomicrograph of a fibrosarcoma which deposits an abundance of collagen stroma. The gross appearance is illustrated in Fig. 6. Note the relative scarcity of cells in proportion to the amount of stroma. The patient was free of sarcoma 5½ years following the surgical extirpation.

Fig. 14.

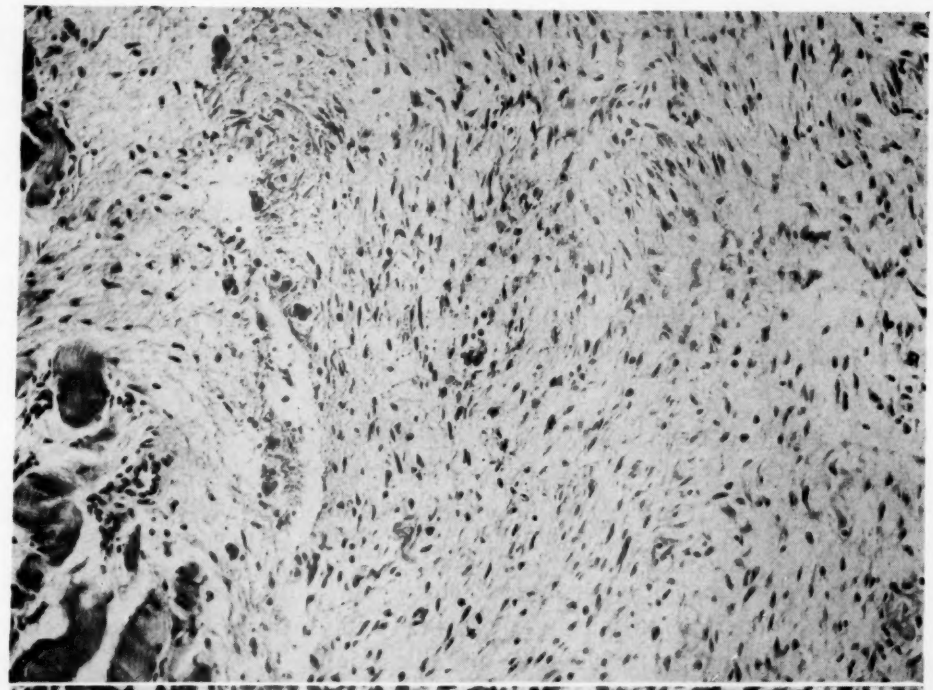


Fig. 15.

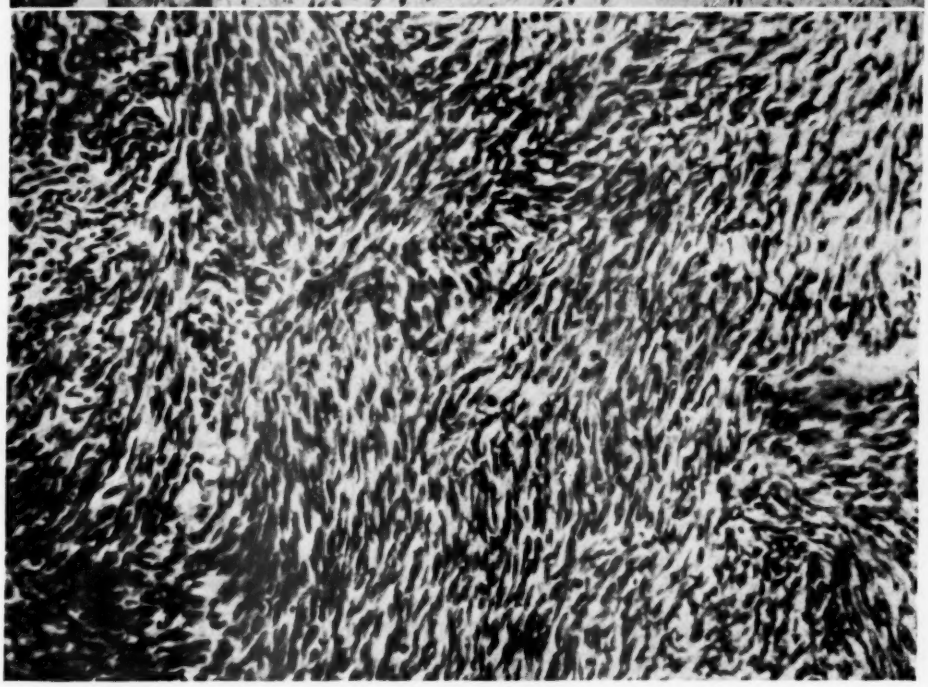


Fig. 14.—Photomicrograph of fibrosarcoma of abdominal wall infiltrating striated muscle.

Fig. 15.—Photomicrograph of a highly anaplastic fibrosarcoma which developed in the left buttock of a 45-year-old woman. The patient succumbed 6 months after onset. Note the highly cellular characteristic with loss of polarity and scanty stroma.

to lose their spindle shapes and become ovoid. Some spindle-cells persist. The nuclei become pyknotic and hyperchromatic. Mitoses may be observed. At the periphery of the tumor some inflammatory reaction with an occasional giant-cell may be seen. Increased tissue edema (probably on the basis of circulatory obstruction), necrosis, and hemorrhage are noted. An increased number of thin-walled capillaries may be observed.

The most anaplastic fibrosarcomas have marked pleomorphism of cells with wide variations in size and shape. Loss of polarity is evident. The nuclei are usually markedly hyperchromatic and both normal and atypical mitoses are evident. No collagen is present and a sparse amount of reticulin is seen. No pseudocapsule is present and there is evidence of patchy necrosis (Fig. 15).

METASTASES

Metastases from fibrosarcomas occur infrequently, although some may metastasize very early. The usual route of dissemination is the blood stream. Meyerding and Pils demonstrated invasion of the blood vessels by soft tissue fibrosarcoma.[49]

The most frequent site for metastases is the lungs and metastases to this site were observed in 9 patients (21 per cent) in this series. Three presented evidence of pulmonary metastases on admission. The average time from treatment at this hospital until pulmonic metastases became evident in the remaining 6 patients was 6.6 months. It thus becomes apparent that a rather small number of fibrosarcomas will metastasize to the lungs in contrast to the frequent metastases to this site from the other sarcomas of the soft somatic tissues (synovial sarcoma, 65 per cent; rhabdomyosarcoma, 39 per cent).

Any organ may be involved by diffuse metastases. Widespread intra-abdominal metastasis was observed in several patients in this series after the disease had become generalized.

Although fibrosarcomas usually metastasize by way of the blood stream, on occasion they may metastasize to the regional lymph nodes. This characteristic must be considered in any therapeutic attack. Stout noted metastases to lymph nodes in 8 per cent of his cases,[72] and involvement of the regional lymph nodes was observed in one instance in our series. Examples of metastases by way of the lymphatics are described by Warren and Sommer,[77] and Hertzler.[38] Wilson reported lymph node metastases in 4 instances.[78]

Metastases have been found in subcutaneous tissues even before pulmonary evidence of metastases is manifest. Wilson quoted two cases in which multiple subcutaneous tumors occurred in widely separated areas undoubtedly as the result of blood stream dissemination. The feature whereby multiple loci of sarcoma may be observed in one extremity (as in one of our patients) invites speculation whether the multiple loci represent metastases from a single fibrosarcoma or whether they are separate, distinct neoplasms. Whichever the explanation, this characteristic of a few fibrosarcomas indicates the necessity for extensive resections in certain instances.

It is of important clinical interest that metastases were noted with relative infrequency (21 per cent) despite the very high local recurrence rate (56 per cent).

ROENTGENOGRAPHIC APPEARANCE

There is no characteristic roentgenographic appearance for fibrosarcoma. The usual finding is a soft tissue density at the site of a soft tissue mass noted clinically. Calcification may be present occasionally, but was not observed in this series and is not considered of clinical import. When fibrosarcomas arise from periosteum they may produce atrophy and invasion of the bone, exhibiting a characteristic picture roentgenographically, or by pressure against the bone they set up a reaction of the bone with cortical ebonization (Figs. 8 and 9).

Metastases to the chest are identified as localized homogeneous shadows with sharply defined borders. They are not infrequently solitary. Any patient with a fibrosarcoma whose roentgenograms show the presence of a discrete density in the lung should be subjected to thoracotomy for possible resection, if the primary tumor is controlled or controllable.

DIAGNOSIS

It is difficult to establish a diagnosis of fibrosarcoma by any means except microscopic examination of the suspected tissue. All superficial or deeper masses of the extremities should be immediately suspected as sarcomas. If an asymptomatic tumor has been present for a rather long time (average 3.5 years), and occurs in the soft somatic tissues of a middle-aged individual, the diagnosis of a fibrosarcoma should be entertained. The usual small size, insidious onset, slow growth, and asymptomatic nature lull suspicion away from the malignant nature of the lesion.

Although roentgenograms do not reveal a characteristic picture they nevertheless do serve to direct the surgeon to the exact site for a biopsy. In those instances of soft tissue masses of the extremities wherein roentgenograms show evidence either of bone invasion or a reaction of the cortex to the irritative phenomenon produced by the tumor, the malignant nature of the neoplasm becomes apparent. There is no method whatsoever to establish the diagnosis of fibrosarcoma except by biopsy.

DIFFERENTIAL DIAGNOSIS

Fibrosarcoma must be differentiated from certain benign tumors, other malignant tumors, and the various non-neoplastic diseases of the soft tissue parts. Benign tumors such as chondromas and osteomas are usually harder and attached to bone. Lipomas are of softer density and are translucent rather than opaque on roentgenographic examination. Synovial sarcomas are more frequent in the hands and feet and usually occur closer to the joints. Liposarcomas are most frequent in the regions of the retroperitoneum, and

shoulder and pelvic girdles. Other malignant neoplasms which must be distinguished include rhabdosarcomas, angiosarcomas, melanosarcomas, and malignant neurilemmomas.

BIOPSY

It is important that facilities be available for the institution of definitive therapy as quickly as possible after the taking of a biopsy.

Aspiration biopsies may be indicated whenever the clinical appearance strongly suggests a malignant neoplasm (large mass with adjacent bone destruction, etc.), and it is desired merely to establish the malignant nature of the tumor before submitting the patient to definitive radical surgery. The advantage of the aspiration biopsy is that it is the least traumatic procedure available. The material obtained by aspiration with a 17 gauge needle may enable the pathologist to classify the neoplasm as benign or malignant, which is all that is expected of the method. Occasionally, the histogenesis of the tumor may be determined, but this is not the purpose of the test and should not be required of it. Any information gained through aspiration biopsy is to the advantage of patient and surgeon, but it should be remembered that fibrosarcomas are usually dense desmoplastic tumors, which do not readily yield tissue to the aspirating needle, and therefore no action should be taken, or conclusions drawn, on the results on a negative test.

A small *incisional biopsy* is indicated when it is necessary to obtain adequate tissue to study the histologic architecture of the mass. A small wedge of tissue should be excised with a sharp scalpel and every effort made to be as atraumatic as possible. No attempt should ever be made to explore into the tumor. Fibrosarcomas are locally excised in toto for histologic study (as practiced for breast cancer), only when the tumor is small, superficial, sharply demarcated, and apparently encapsulated.

On the Mixed Tumor Service of the Memorial Hospital a method has been adopted which combines the biopsy performance with the institution of definitive surgery at the same operative séance. The procedure was developed in the hope that dissemination of tumor emboli resulting from the trauma of the biopsy could be held at a minimum. The method is as follows: A tourniquet is placed proximal to the lesion, an incisional biopsy is performed, and a frozen section studied. If the report is a benign tumor, a local excision is effected and the tourniquet removed. If the report is fibrosarcoma, a wide resection is completed, and if an amputation is necessary, another tourniquet is applied proximal to the one already present and the amputation effected between the tourniquets. This procedure has been adopted because of the observation that following the trauma incident to local excision of certain sarcomas, the postoperative course is sometimes complicated by the presence of pulmonary symptoms. In these cases chest roentgenograms reveal patchy, mottled areas which are diagnosed either as bronchopneumonia or pulmonary infarcts. These patients usually return at later dates with definite pulmonary metastases present at the very sites where the postoperative roentgen appearance of the lung lesions was due to tumor emboli showered there as a result of the

surgical trauma to the primary neoplasm. The tourniquet biopsy and amputation is performed in an attempt to prevent the vascular spread of such embolic showers.

PROGNOSIS

The over-all end results following the treatment of fibrosarcomas are better than for other types of sarcomas. Earlier diagnoses and the institution of radical surgical treatment no doubt will improve the survival rate of patients bearing fibrosarcoma. The data of this series accordingly are analyzed to note those factors which may have influenced the five-year cure rate. The time that the patients were treated at the Memorial Hospital is used as the base line for computing survival periods.

Recurrence Rate.—Fibrosarcomas are notorious for the high incidence of recurrences which develop subsequent to initial attempts at extirpating the neoplasms. The data are summarized in Table IV. Of the 39 patients observed here 22 (56 per cent) developed recurrences. The average duration from the onset of treatment until a recurrence became clinically evident was 8.6 months. The observation that 9 of these 22 patients developed their recurrences less than two months after the attempt at local extirpation indicates inadequacy of the primary surgical attempts. These values include all attempts at excision of the tumor including office procedures by private doctors. The high recurrence rate emphasizes the futility of attempting excision except under the most favorable hospital conditions with a competent pathologist in consultation and with the surgeon prepared to perform the most radical surgery when indicated. Inadequate excision traumatizes the tumor, always results in recurrence, and possibly enhances the occurrence of metastases.

TABLE IV. RECURRENCE RATE OF FIBROSARCOMAS

Total number of patients	39
Number who developed a recurrence of fibrosarcomas	22
Percentage who developed a recurrence	56%
Duration in months from treatment until recurrence	8.6
End results of patients who developed a recurrence:	
(a) Number who died	5
(b) Duration in months from treatment of recurrence until death	10
(c) Number who survived 5 years without evidence of fibrosarcoma	5
(d) Percentage who were without evidence of fibrosarcoma 5 years or more after treatment of recurrence	50%

It is not uncommon for a second, and at times a third, recurrence to develop following incomplete attempts at extirpation. The usual prolonged time (average 1.5 years) intervening before the onset of a second or third recurrence indicates the relatively benign nature of some of these neoplasms. Stout[72] reports a recurrence rate of 60 per cent of soft tissue fibrosarcomas. Taylor and Nathanson[73] record 256 cases of which 159 recurred after one or more excisions elsewhere. Carroll and Martin[15] record 15 per cent of their

40 cases as recurrent neoplasms when the patient first applied for treatment. Wilson[78] described 33 patients who have had recurrent tumors in a total of 207 patients. Bick[8] and Burke[13] also stress the high recurrence rate.

Recurrences most likely develop as a result of pseudopodium-like extensions of the fibrosarcoma through its capsule which persist when excision is limited to decapsulation. Recurrences may also develop as the result of autoinnoculation or implantation at the time of surgery due to spillage of tumor cells into the wound. Harrell and Valk[36] have reported an accidental autogenous transplantation of an ulcerated fibrosarcoma of the heel during the application of a pedicled skin graft. They believe this due either to direct extension of the tumor through the graft or by accidental contamination of the incision at the donor site with tumor cells. Greene[32] has successfully transplanted human fibrosarcomas into the anterior chambers of the eyes of guinea pigs and carried them through numerous generations.

Influence of Age on Prognosis.—In Table V it is apparent that the survival rate is higher in the two age extremes. Thus the 2 patients under 20 years of age, and the 1 over 50 years, each survived the five-year period of definitive cure. The group between the second and the third decades apparently had the poorest prognosis, for 2 patients between 21 and 30 years of age both succumbed to this disease and 3 of the 7 between 31 and 40 years of age, died. Fibrosarcoma is thus different from synovial sarcoma where no patient over 50 years of age survived, and the survival rate was much higher in the younger age group.

TABLE V. INFLUENCE OF AGE ON THE FIVE-YEAR SURVIVAL RATE OF PATIENTS WITH FIBROSARCOMA

AGE IN YEARS	NUMBER OF PATIENTS	NUMBER OF FIVE-YEAR CURES	PERCENTAGE OF FIVE-YEAR CURES
Under 20	2	2	100
21-30	2	0	0
31-40	7	4	57
41-50	4	3	75
51-60	1	1	100
61-70	2	0	0

Influence of Sex on Prognosis.—Women apparently enjoyed a higher incidence of five-year cures. Thus 6 of the 10 patients who were apparently free of disease 5 years after therapy were women. The difference is so small that it has no statistical significance.

Influence of Location of Tumor on Prognosis.—Table VI reveals that five-year cures were most numerous in those patients with fibrosarcomas of the foot, buttock, and torso. Four patients with fibrosarcoma of these locations each survived 5 years or longer without recurrence. Fibrosarcomas of the arm and the thigh each offered a 50 per cent five-year survival rate and 5 patients bearing the fibrosarcomas about the shoulder including the scapular region had a five-year survival rate of 40 per cent. One patient with fibro-

sarcoma of the leg succumbed to recurrence. The Mayo Group and others reported a somewhat poorer prognosis for fibrosarcomas of the lower extremities than of the upper extremities.[50]

TABLE VI. INFLUENCE OF LOCATION OF FIBROSARCOMA ON THE FIVE-YEAR SURVIVAL RATE

LOCATION	NUMBER OF PATIENTS	NUMBER OF FIVE-YEAR CURES	PERCENTAGE OF FIVE-YEAR CURES
Upper extremity	9	4	44.4
Hand	2	1	50.0
Arm	2	1	50.0
Shoulder (including scapular region)	5	2	40.0
Lower extremity	8	5	62.5
Foot	2	2	100.0
Leg	1	0	0.
Thigh	4	2	50.0
Buttock	1	1	100.0
Torso (chest wall, back and abdominal wall)	1	1	100.0

Influence of Symptomatology on Prognosis.—The majority of patients in this series had as their initial symptom the presence of a painless mass. For the 33 patients whose first symptom was the presence of a painless mass, the average delay before seeking treatment was 29 months. In this group the five-year cure rate averaged 68 per cent.

Three patients complained of a painful mass as the initial symptom and they presented themselves for treatment an average of 3.7 months after the onset of the symptoms. Of these 3 patients, 1 died 4 months after admission, 1 was lost to follow-up after 1 year of treatment with no evidence of fibrosarcoma at the time, and the third is well 20 years after treatment.

Of the patients who complained of pain as the initial symptom, 2 of the 3 died within 1 year after admission and the third is well 6 years after treatment. The fact that the pain heralded the onset of fibrosarcoma suggests that the lesion may have been present for a long time in the depths of the tissues and therefore a long and hazardous time elapsed before the patient was cognizant of the presence of a tumor. The outcome under these circumstances would not be expected to be favorable. It is worthy of observation that whenever the initial symptom was the presence of a painless mass, the culpability for delay lay with the patient who neglected the slowly growing asymptomatic mass for a long time before seeking medical attention. On the other hand, the patients who suffered pain as the initial symptom usually sought medical advice quickly, but the culpability for delay in establishing the correct diagnosis lay usually with the medical profession.

Influence of Type of Treatment on Prognosis.—Until recently, reliance was placed usually upon simple excision, either alone or in conjunction with some form of radiation therapy; or upon radiation therapy by itself as the treatment of choice for fibrosarcoma. This conservative treatment, combined with the fact that an unduly long time had elapsed before therapy was instituted, would preclude expectations for good results. However, Table VIII, in which

the type of therapy is analyzed to rate the ability of the different methods in effecting a cure, reveals interesting data. Of the 4 patients who were subjected to surgical treatment alone, all survived the five-year period of definitive cure. Of the 2 patients whose fibrosarcomas were resected, and the surgical treatment followed by postoperative irradiation, 1 survived the five-year period; and of the 4 patients who received irradiation followed by surgical resection of their tumors, the five-year cure rate was 75 per cent. In all fairness to the choice of therapeutic procedures, it should be stated that the prognosis for the fibrosarcomas receiving preoperative irradiation was clinically adjudged to be less favorable than for those for which operation was the primary procedure. There were 6 patients who received irradiation alone at Memorial Hospital and of these 5 (83 per cent) survived 5 years without evidence of neoplasia. All 6 had undergone local excision of the fibrosarcomas elsewhere before they were admitted to the Memorial Hospital where irradiation was given to the site of the previous local excision as a prophylactic measure. Hence, no claims can be made for the role which irradiation may have played in effecting the cure.

TABLE VII. EFFECT OF THE TYPE OF TREATMENT AT THE MEMORIAL HOSPITAL ON THE FIVE-YEAR SURVIVAL RATE OF PATIENTS WITH FIBROSARCOMA

TYPE OF TREATMENT	NUMBER OF PATIENTS TREATED	NUMBER OF FIVE-YEAR CURES	PERCENTAGE OF FIVE-YEAR CURES
Surgery			
Excision	3	3	100
Amputation	1	1	100
Surgical resection and postoperative irradiation	2	1	50
Irradiation followed by surgical resection	4	3	75
Irradiation	6	5	83
No definitive treatment	4	0	0

One patient (Case 31) had a fibrosarcoma, Grade III, of the left forearm including the ulnar bone which was diagnosed six weeks after birth; the tumor was treated by high voltage x-rays and Coley's toxin and the patient was free of evidence of sarcoma 4 years after treatment. The radiation therapy consisted of x-rays generated at 250 kv. with 30 Ma., 1½ mm. copper filtration, target-skin distance of 50 cm., 250 r per day to the right forearm posteriorly for a total dose of 2,000 r in air, followed by 250 r daily to the right forearm anteriorly for a total dose of 1,500 r in air. The calculated tumor dose was 3,360 r. He was then given a course of Coley's toxin. The mass subsided. Roentgenograms of the involved bone showed marked improvement and the patient when last seen (4 years after treatment) revealed no evidence of fibrosarcoma; muscular atrophy of the extremity was present but no loss of strength was noted (Fig. 2).

One helpful result of the analysis of this data has been our conclusion that in the past, radical surgical measures have been applied too late. Of the 39 patients observed, 28 had received some form of treatment elsewhere before

coming to the Memorial Cancer Center for therapy. Of this group, 20 patients had recurrent operable lesions and in 4 (10 per cent), only prophylactic x-ray treatment was given. Four additional patients were admitted to this institution after undergoing therapeutic attempts elsewhere, but the fibrosarcomas were too widely metastatic to warrant definitive therapy. In only 11 cases (28 per cent), did the patient come with a primary operable neoplasm. The observation that 20 patients presented themselves after having had 1 or more recurrences following improper surgical extirpation indicates that this neoplasm is rather kind to both the patient and surgeon, and as a rule lends itself to resection even though traumatized by previous inadequate attempts at surgical extirpation.

Irradiation has little to offer in effecting cures for fibrosarcomas, for they are usually radioresistant.

Influence of Previous Treatment on Prognosis.—In only 3 of the 20 patients available for follow-up study was the initial treatment given at Memorial Hospital, and all three enjoyed a five-year cure rate. Of the 17 patients who were initially treated elsewhere 11 (64 per cent) remained free of fibrosarcoma for 5 years or longer. This high survival rate which was obtained despite previous inadequate and often repeated treatment elsewhere resulting in one or more recurrences, indicates the relative benignity of fibrosarcomas but emphasizes strongly the inadequacy of the surgery practiced by so many in treating this malignant neoplasm.

Influence of Degree of Malignancy on Prognosis.—The most important prognostic guide is the degree of malignancy manifested by the microscopic appearance. In each instance in this series when the histologic examination revealed a high degree of malignancy (Broders: Grade III or IV), the clinical course was characterized by early and widespread metastases and usually rapid death of the patient. The series from the Mayo Clinic clearly corroborates the prognostic significance of the degree of anaplasia of fibrosarcoma.[42, 50]

From this analysis it may be concluded that such factors as age, location, duration, symptoms, etc., play a relatively minor role in effecting the prognosis of patients with fibrosarcoma. This is evidenced by the usually long delays before treatment, and the high recurrence rate following inadequate treatment, but notwithstanding, the quite high over-all five-year survival rate. In most cases, the histologic appearance of the tumor signified a low-grade malignancy. Contrariwise, those patients who reported for treatment early because of rapid growth of the tumor and usually died despite early radical treatment revealed a highly anaplastic neoplasm on microscopic study. Fortunately, this type was infrequently encountered (4 times).

END RESULTS

Of the 39 patients observed at the Memorial Hospital 13 are alive and apparently free of fibrosarcoma. The end results are tabulated in Table VIII. Of the 39 patients only 22 were suitable for evaluation of a five-year survival rate because 17 patients were observed too recently, that is, within the past

5 years. Of the 22 patients treated more than 5 years ago, 13 are alive and have been free of fibrosarcoma 5 years or longer. The absolute five-year survival rate, accordingly, is 59 per cent. Of this group, 4 patients survived from 5 to 10 years, and an additional 4 survived for 10 to 15 years, and there were 2 instances in which the patients survived without evidence of recurrent fibrosarcoma for a period of over 15 years.

TABLE VIII. FIVE-YEAR END RESULTS IN CASES OF FIBROSARCOMAS STUDIED AT THE MEMORIAL HOSPITAL, NEW YORK, N. Y., 1931 THROUGH 1948

Total number of patients	39
Number used to compute 5 year survival (Seventeen patients were treated too recently to be considered in the 5 year survival rate)	22
Number alive and free of fibrosarcoma* 5 years or more after treatment	13
Absolute 5 year survival rate	59%
Number of patients lost to follow-up before 5 year period Case 1, well for 1 year, lost to follow-up Case 14, well for 1 year, lost to follow-up	2
Relative 5 year survival rate (Patients lost to follow-up subtracted from total number of patients)	65%
Number of patients on whom a curative procedure was attempted at the Memorial Hospital (Four patients when first observed suffered from pulmonary metastases and either no treatment or palliative radiation therapy was given)	18
Number of patients used to compute therapeutic 5 year survival rate (Patients lost to follow-up [2] and those patients on whom no curative therapy was applied [4] are subtracted from all the patients in the series	16
Therapeutic 5 year survival rate	81.3%

*Two patients recorded as failures are alive but with persistent fibrosarcoma 6 years (Case 12) and 8 years (Case 19) after treatment.

Of the 22 patients who were treated over 5 years ago, 2 were lost to follow-up study. One of these patients, who had a local excision performed elsewhere and received postoperative radium element pack treatment at Memorial Hospital, was well and free of disease one year after therapy, but refused to return or to answer any of the correspondence pertaining to follow-up data. In the second patient, an excision of the tumor followed by postoperative x-ray therapy was accomplished and he remained well one year after treatment but refused to return for follow-up studies. Since it is not possible to know the final outcome of these cases they may be excluded from the number of cases considered for follow-up evaluation. The relative five-year survival rate is 65 per cent.

In order to adjudge the efficacy of the therapeutic attempts at this hospital and to establish a therapeutic five-year survival rate, 4 additional patients are excluded from the calculations because when they first presented themselves at this institution they had detectable pulmonary and generalized metastases. These patients accordingly received no definitive therapy, and either palliative therapy was administered to the metastases, or no treatment

whatsoever was given. Therefore, in only 18 of the 22 cases were curative procedures instituted. Of these, 2 were lost to follow-up, which leaves a total of 16 patients, with the therapeutic five-year survival rate for this series, 81.3 per cent.

This high cure rate despite delays in diagnosis and treatment, and trauma induced by previous inadequate surgical procedures, indicates that fibrosarcomas lend themselves well to cure. Reports in the literature giving poor end results in the treatment of fibrosarcoma are due undoubtedly to the inclusion of other sarcomas under the heading of fibrosarcoma. Thus, Nathanson and Welch,[54] report that 63 per cent of their patients succumbed. Stout emphasizes the lack of great malignancy in this tumor by stating that of 144 cases of fibrosarcoma of the soft parts of which 107 were followed, in only 20 per cent did death occur as a result of tumor. He states moreover, that the figures for fibrosarcoma of all parts are comparable. Heller and Sieber[37] report on 60 patients of whom 37 were followed until death, 12 were living, and no follow-up information was available on 11. Wilson,[78] of Duke University, reported on 111 patients with fibrosarcoma, in which group the mortality rate was 62.2 per cent, 29.7 per cent were well and 8.1 per cent were still living with residual fibrosarcoma. Ivins, Dockerty, and Ghormley,[42] reported the experiences at the Mayo Clinic with fibrosarcoma of the soft tissues of the extremities, and found that the five-year survival rate for patients with fibrosarcoma regardless of the pathologic grade of the tumor and of the form of the treatments employed was 38 per cent. They have classified the relative grades of malignancy according to the method of Broder, based on the histopathologic structure of the tumor, and have revealed that in 8 patients with tumors classified as Grade I, the average survival was 38 per cent; in 8 patients with tumors classified as Grade III, the average survival was 31 per cent and in 2 patients with tumors classified as Grade IV, the average survival for five years was 20 per cent. They stress the prognostic value gleaned from the classification of the tumor along with the histopathologic estimates of malignancy.

TREATMENT

The treatment of fibrosarcoma revolves about one of three major disciplines:

1. The treatment of the primary lesion when no metastases exist.
2. The treatment of the primary lesion when regional metastases are present.
3. The treatment of metastases which appear after the primary lesion has apparently been controlled.

Treatment of Fibrosarcoma Without Metastases.—Various therapeutic measures have been utilized: (1) local surgical excision, (2) amputation of the involved extremity, (3) external roentgen irradiation, (4) teleradium therapy, (5) interstitial radon irradiation, and (6) some combination of these methods. Although one cure apparently has been obtained with radiation therapy in

this series it is our studied conviction that this type of treatment should never be used as the modality to effect a cure. Adequate surgical resection is the only suitable method for the treatment of fibrosarcoma. The extent of the resection depends upon the stage of the tumor and its location. The high frequency of local recurrence so often observed (57 per cent) indicates the futility of treating this malignant neoplasm in an office procedure by local excision. The two proper surgical approaches consist of (1) a radical surgical extirpation which includes a wide margin of approximately 4 to 6 cm. of the tumor bed surrounding the neoplasm; and (2) amputation of the involved extremity as the only alternative when the first procedure is not feasible.

Whenever fibrosarcomas involve the shoulder girdle or the pelvic girdle, i.e., are located above the shoulder or hip joints, or involve muscles which originate above these joints, the amputation must, of necessity, be extensive and consist either of an interscapulothoracic amputation or a hemipelvectomy. Each of these procedures has been performed by us in the treatment of fibrosarcoma.

The surgeon should be guided by histologic examination of the resected specimen and if the biopsy reveals an anaplastic, highly malignant neoplasm it is believed that nothing less than an amputation of the involved member can effect a cure unless the tumor is so located that an extremely wide surgical extirpation can be effected. Thus if the tumor is located within certain muscles the excision of the entire group of muscles from their origin to their insertion must be accomplished.

When the neoplasm arises from periosteum and infringes on bone, the safest procedure is an amputation. For those neoplasms which present a highly differentiated histologic appearance, a segmental resection of the involved bone with splinting of the defect with a bone graft may be performed. Any fibrosarcoma which has infringed upon a joint should be treated by amputation.

Wide local excision may be attempted in those instances where the tumor has wrapped itself about a major blood vessel or nerve trunk. Because some fibrosarcomas grow in an expansile manner, in certain instances the neoplasm may be dissected free from nerve or artery. If the fibrosarcoma is of low-grade malignancy but infiltrative, a major blood vessel may be resected and the defect bridged by an arterial graft.

Fibrosarcomas which develop in irradiated tissue should have all the damaged tissue included in the resected specimens. Emphasis must be directed to resection of adequate tissue about the fibrosarcoma. Inasmuch as fibrosarcomas metastasize so infrequently to lymph nodes, it is not considered necessary to include a lymph node dissection in all cases. However, since it does occur (5.1 per cent in this series; 8 per cent in Stout's series) when the neoplasm is located close to the regional lymph nodes, the latter may be excised in continuity with the primary tumor. This procedure should be performed, of course, wherever nodal metastases are clinically evident.

We do not consider irradiation of value in effecting a cure, although in one case of this series a cure was obtained by means of roentgen therapy.

Hence if the patient refuses surgery, irradiation may be administered in certain instances. We do not use it postoperatively, but rely upon adequate surgery for the cure.

In those instances in which a local excision had been performed, usually by the family doctor, and the patient then referred to a cancer clinic after the malignant nature of the tumor had been discovered, it was the practice at the Memorial Hospital in past years to administer a full course of irradiation to the operative site. More recently the policy is to perform a wide surgical resection of the previous operative site, and the number of cases wherein residual sarcoma is found certainly justifies the procedure. A review of the literature shows that relatively few patients have been subjected to radical surgical treatment early in the course of their fibrosarcomas. The combination of a small tumor, mild symptoms, and slow growth makes the surgeon reluctant to perform radical surgery.

Treatment of Primary Fibrosarcoma and Regional Lymph Node Metastases.—An important method of therapy for a situation in which neoplastic involvement of the regional lymph nodes accompanies the primary fibrosarcoma is radical excision of the primary and lymph node bearing regions en bloc. The method for attempting a cure in those instances in which involvement of the upper portion of the extremities requires such procedures as hip joint disarticulation or shoulder (interscapulothoracic) disarticulation is to perform a radical groin or lower neck dissection, respectively, associated with the amputation. Whenever the fibrosarcoma is located on an extremity but proximal to the elbow or knee with axillary or inguinal metastases present, and the primary tumor is movable and suitable for radical local excision, the ideal treatment would be an excision and dissection in continuity to encompass the primary site, the regional lymph nodes, and the intervening tissues, namely, skin, fat, fascia, and lymphatics.

Treatment of Metastases When the Primary Neoplasm Is Controlled.—When regional lymph nodes are invaded by fibrosarcoma, the treatment of choice is radical dissection of the lymph node bearing region, when technically feasible, after the manner described previously, that is, in continuity with the primary lesion or in conjunction with amputation. If the fibrosarcoma has become fixed to the parietes, has invaded the vessels or the contiguous bones, radical amputation must be performed.

Solitary Metastasis to the Lung.—Success is being achieved in the partial or complete resection of a lung bearing fibrosarcomatous metastases. Alexander[2] had reported that the best results obtained in the treatment of metastatic cancer to the lungs were in metastases from fibrosarcomas. Thus, any patient who had successful local treatment for a fibrosarcoma and develops metastases in one lung, should receive the benefit of thoracotomy and a lobectomy or pneumonectomy as indicated. The unilaterality of pulmonary metastasis should be confirmed by tomographic studies. If a patient presents a solitary pulmonary metastasis when he first presents himself for treatment of a sarcoma of the soft somatic tissues, the presence of the metastasis should not deter the surgeon from treating the primary tumor as if no metastasis was

present. We have performed thoracotomies, segmental resections, and lobectomies for pulmonary metastases from other sarcomas with good palliation and we would do it for fibrosarcomas.

Palliative Therapy.—Deep x-ray therapy, in our experience, has offered good palliation. Symptoms arising from pulmonary or skeletal metastases have sometimes responded well to a palliative course of irradiation. Although fibrosarcomas are highly radioresistant neoplasms and no reliance should be placed on irradiation for cure, no patient should be denied this modality for palliation, which at times may be excellent.

Coley[16] has reported good results in certain instances with combined interstitial and external irradiation. No beneficial results have been observed from the use of radioactive isotopes, chemotherapy, or hormonal administrations. One of our patients received a protracted course of treatment with ACTH, without modification of the course of the disease.

SUMMARY

The pathologic and clinical features of thirty-nine cases of fibrosarcoma are analyzed and presented. These cases were observed from 1931 to 1948 inclusive, and constituted 5.4 per cent of malignant neoplasms of the soft somatic tissues studied on the Mixed Tumor Service of the Memorial Hospital.

As a rule, no etiological factors were established in this series although in several cases trauma, scars from burns, scars from abdominal incisions, a congenital relationship, and sarcoma developing in myositis ossificans and in irradiated tissues were observed.

There was a preponderance of women in our patients. Fibrosarcoma is essentially a disease of younger adults; the average age was 39.4 years. Fifty-three per cent occurred in patients between the ages of 30 and 50 years.

The tumors most frequently occur in the proximal portion of the extremities. The most frequent sites for this series were the shoulders and thighs.

The usual history is one of a long period wherein a tumor grows slowly over many years. There was no characteristic symptom complex or radiographic characteristic noted in this series. The diagnosis must be established by biopsy. Metastases from fibrosarcoma occur relatively infrequently. The most frequent site is the lung, where metastases were observed in 21 per cent of this series. If the tumor is of a metastasizing variety, metastasis will usually develop early in the clinical course.

Local recurrences were observed in 56 per cent of this series, usually because of inadequate initial surgical excision. The absolute five-year survival rate is 59 per cent. The relative five-year survival rate is 65 per cent, and the therapeutic five-year survival rate is 81.3 per cent.

Radical surgical excision is the one suitable method of ablating fibrosarcoma. Radiation therapy may be used to supplement surgical treatment, or for palliation.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

SURGERY IN VIENNA

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TWO-thousand-year-old surgical instruments at the Roman museum in Vienna are indications of some of the earliest surgery on Viennese soil. Medieval Vienna also had its surgeons. In the archives of the University one may find the names of various subordinate medical personnel who undertook voluntary examination by the medical faculty to permit their classification as Wundharzt, Bruch- or Steinschneider.† The activities of the Wundharzt and Bader were limited to the purely manual approach in the care of wounds. Most local Wundharzt came from Italian surgical schools, and they were preferred to those who were trained under a German Master. The Wundharzt did not enjoy a very favorable position, and their roving habits and somewhat charlatan-like behavior did not foster equality with the internists. In those days no physician—that is to say, internist—ever took scalpel in hand.

Because of the impudence of these practitioners, the medical dean, Johann Wilhelm Mannagetta (1588-1666) was compelled in 1650 to interfere in the affairs of the Collegium Chirurgicum. This impudence apparently consisted in visiting their patients on horseback, rather than on foot. After a certain amount of strife, it was concluded that the Wundharzt should again visit their patients, modestly, on foot. Aside from these Wundharzt who were considered an inferior group of practitioners, there were also Schneidharzt who possessed complete technical training and contained among their group many skillful operators. Until the sixteenth century they carried out the anatomic dissections in Vienna, supervised, however, by a physician. At the same time, toward the end of the sixteenth century, there were physicians who practiced theoretic surgery and possessed the title of doctor in medicine and surgery. Although

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†Translator's note: Many of these titles are difficult of translation. The Wundharzt was most comparable to the Barber-Surgeon. The Steinschneider and the Bruchschneider were lithotomist and herniotomist respectively. The Schneidharzt appears to have been a combination of anatomy prosector and primitive surgeon. His work included amputation, excision of tumors, and such operative therapy as was practiced at that time. Schönbauer in *Das Medizinische Wien* states that surgeons, barbers, and bath attendants (Bader) all took part in the treatment of wounds, but were members of different guilds. Thus hair trimming was the privilege of the barber. Although at one time the Bader was permitted only minor surgery (treatment of wounds and ulcers, cupping, the application of leeches, venesection) and more serious surgery required the Schneidharzt, this distinction gradually disappeared. In official positions in the hospitals and in the army they held equivalent rank. To be certain of an income, the surgeon or Schneidharzt learned the trade of barber or bath attendant, and endeavored to obtain, by purchase or marriage, a barbershop or bath.

some of these men may have been extremely capable—in those martial days there was no lack of work for the surgeon—there were none who were of significance beyond their narrow circle.

Although reform in medical education began under the wise leadership of the Empress Maria Theresa (1717-1780), the necessity for the instruction of students concerning surgical problems was not given adequate consideration. A surgeon was given the duty of teaching the entire field of surgery and the art of dissection in a single school year. In 1751, Franz Joseph Jaus (1696-1771) was given the first independent chair of theoretic surgery.

Ferdinand Leber (1727-1808) was perhaps the first surgeon to practice his specialty as a science. He was born in Vienna, the son of a wigmaker and a midwife, apprenticed himself to a Wundharzt, and continued his training under the medical faculty which, in 1751, awarded him the title of Master. After the completion of his training he was named surgeon to the Bürgerspital and simultaneously was placed in a supervisory capacity over the two large suburban hospitals, the Marxer-Spital, and the Bäckenhäusl. After 1756 he also operated at the Internal Clinic of Anton de Haën (1704-1776) and was finally made a member of the faculty. In 1761 he was nominated the successor of Jaus as professor of anatomy and theory of surgery. He gave up his anatomical lectures in 1786, and until his death, devoted himself entirely to surgery. Leber did not have a surgical clinic at his disposal and practical instruction was first given after 1774 by the clinical professor, Raphael Steidele (1737-1823) at the newly founded Obstetrical and Surgical Clinic in the Unierten-Spital. Among Leber's numerous contributions, his treatment of aneurysms found widest acceptance in the international literature. At that time aneurysms of the brachial artery were of daily occurrence as a result of unskillful venesection. Although in antiquity (Antyllus, second century A.D.) aneurysms were treated by combined distal and peripheral ligation, they were later treated conservatively, as a rule, by the use of cold, or more radically, by cautery.

Leber, and independently also Johann Christian Theden (1714-1797), and Carlo Guattani (1707-1771) came upon the thought in 1770 that not only the aneurysm, but also the peripheral artery should be compressed. Leber soon recognized the great significance of arterial compression and suggested its use to the exclusion of other methods. With this principal advance a new impetus was given to operative treatment: in 1785 John Hunter (1728-1793) ligated the vessel leading into the aneurysm above the diseased area. Leber also played a significant role in a field distant from surgery. In 1757 he was given the duty of being present during judicial torture proceedings. He frequently saw "that a truly courageous criminal could undergo extremely painful torture and insist upon his innocence, while the innocent, overcome by the severity of pain, would frequently confess to crimes that he had not committed." With the aid of Joseph Sonnenfels (1732-1817), he was successful in obtaining the abolition of torture in Austria.

In 1785 Emperor Joseph II (1741-1790), authorized the establishment of a medical-surgical military academy for the purpose of obtaining better care for sick and wounded soldiers. A medical faculty for the institute was also

authorized, and this was one of the deciding steps which brought surgery to a level with internal medicine. The first surgeon of this institute was Johann Hunczowsky (1752-1798), who acquired additional training in foreign countries, but because of his generally conservative turn of mind, did not contribute particularly to the development of his specialty.

His successor, Christoph Bonifacius Zang (1772-1835), was also a follower of conservative methods. His reputation was largely made through his treatment of fractures by simple suspension apparatus—a precursor of our modern traction methods.

With the opposition of Zang, Vincenz von Kern (1760-1829), Steidele's successor, whose influence was more marked in the field of obstetrics, could hardly succeed in his attempt to effect one of the most important revolutions in surgery. Until the end of the eighteenth century, surgeons had destroyed the good results of their treatment of wounds by a polypragmatic attitude: Wounds were stuffed with charpies, bandages were changed frequently; at each bandage change the wound was industriously probed and again filled with a dry or salve covered charpie, then rebandaged or placed in plaster. This procedure, together with venesection, vomitants, purgatives, enemas, etc., did not contribute particularly to the well-being of patients. Kern recognized the error of such treatment and recommended, in 1809, immobilization, proper positioning, and the open treatment of wounds, usually with simple compresses. Inasmuch as Zang had suggested in 1809 "one should attend to the closure of wounds, the removal of damaged tissue, the preservation of the remaining parts, and the amputation of lost tissues," it is difficult today to understand the fruitless opposition to Kern's ideas.

Through the foundation of an Operateur-Institute, Kern became responsible for the further development of capable Austrian surgeons, as before this time specialist training had to be sought in foreign countries.

In 1824 Kern was succeeded by Joseph Wattmann (1789-1866). As far as I have been able to discover he was the first to recognize air emboli in their importance as operative accidents in surgery of the extremities, and to suggest compression of the central veins as therapy. An example of his surgical ability was his attempt at arthroplasty for ankylosis of the elbow. The gradual increase in the size of the student body made it necessary to create a Second Surgical Clinic. This chair was given to a pupil of Wattmann, Franz Schuh (1804-1865), in 1841. Schuh's most significant contribution was the introduction of physical diagnosis to surgery and its development for the problems peculiar to surgery, as Josef Skoda had done in internal medicine. Perhaps it might be more accurate to say that he recognized Skoda's contribution and saw its applicability to surgery. Schuh frequently carried out thoracentesis, and, in 1840, suggested puncture of the pericardium. A few weeks after the Boston announcement of ether anesthesia it was introduced in Austria by Schuh. In 1862, he blamed the appearance of postoperative chills and fever on the appearance of pus and putrefaction, influenced markedly by Ignaz Philipp Semmelweis (1818-1865).

Wattmann was succeeded by his pupil, Johann von Dumreicher (1815-1880) in 1849. The latter was one of the first in Vienna to interest himself in orthopedic problems. Dumreicher was a good surgeon, but too attached to older methods to be able to bring much that was new into surgery.

After Schuh's death, Theodor Billroth (1829-1894) was made the head of the Second Surgical Clinic in 1867. His amazing personality brought Viennese surgery from mediocrity at a single stroke. He introduced in Vienna, as he had in Zurich, Rudolf Virchow's (1821-1902) new trends in research, both by numerous valuable contributions of his own, and above all by bringing research mindedness to his assistants and operateurs. The comprehensive reports concerning his clinical material, so ably analyzed by him, were in the nature of a novelty to Vienna. It was clear to Billroth, as to so few of his contemporaries, that unless the complex problems of suppuration, fever, and wound complications were solved, further development in surgery was not possible. In 1874, as a result of five years of most careful work, there appeared *Untersuchungen über die Vegetations formen von Coccobacteria septica und den Antheil, welchen sie an der Entstehung und Verbreitung der accidentellen Wundkrankheiten haben* (Investigations of the Vegetative Forms of *Coccobacteria septica* and the Role They Play in the Origin and Extension of Accidental Wound Complications). He came, however, to the conclusion that the bacteria had no pathologic significance; rather, that the extension of inflammatory processes was due to a ferment-like substance, the so-called zymoid. While the fallacy of this point of view was soon recognized, the work constituted an impetus to further study. Robert Koch (1843-1910) wrote to him: "When I began my first investigations I was entirely under the influence of your studies of the *Coccobacteria septica,* which had been published at that time, and to the present day I have not lost that impression."

Billroth's experiences caused him to be somewhat tardy in recognizing the necessity of Lister's treatment, but with this recognition there was a change in the direction of his surgical activity. Previously his chief activities were in the surgical realm of lower jaw resections, resection of the esophagus, and extirpation of the larynx; operations in which the long-term success was dubious because of the malignancy of the process. At the peak of his ability, and under the protection of antisepsis, Billroth could begin his chief work—the surgery of the gastrointestinal tract—and complete it successfully. After his assistants, Carl Gussenbauer (1842-1903) and Alexander von Winiwarter (1848-1917), had worked out the method on dogs, Billroth performed the first successful pylorus resection in 1881. While neither the idea nor the first application of the method was Billroth's, it was in his fortunate hands that the method became practical.

Gastroenterostomy, developed by Billroth's pupil, Anton Wölfler (1850-1917), after a suggestion by Karl Nicoladoni (1847-1902), was the foundation for Billroth's second method for resection of the stomach (1885). Billroth performed a gastroenterostomy for an apparently inoperable carcinoma of the stomach. As the operation progressed it seemed that the tumor was operable,

and he resected the stomach, closing the duodenum and the cut end of the stomach blindly, leaving the gastroenterostomy in place. The patient died four months after operation with generalized metastases. Despite this, the method had demonstrated its practicability. The method, later known as the Billroth II, was slow to become popular until cautious modifications eliminated its drawbacks.

A contemporary of Billroth, Eduard Albert (1841-1900), became Director of the First Surgical Clinic in 1881. Although his fame was overshadowed by the magnificent personality of Billroth, it should not be forgotten that many advances in surgical technique are to be credited to him. He was the first to use nerve transplantation; he was the first in Austria to perform thyroidectomy and nephrectomy; was interested deeply in joint mechanics, and stimulated his pupil, Adolf Lorenz (1854-1946), to the development of orthopedics as an independent field. As the result of his historical studies, he reintroduced the aneurysm operation of Antyllus after it had been forgotten for fifteen hundred years.

In 1880, Albert expressed the opinion that survival prospects for carcinoma of the stomach would be considerably increased by extensive resection, preferably total gastrectomy. As he thought that the direct suture of the esophagus and duodenum impossible, he suggested that the cardia be closed blindly and that the duodenum be brought out to the abdominal wall as a feeding fistula. He demonstrated the feasibility of his suggestion in animals and on cadavers, but was unable to find a case suitable for operation. Until the advent of our present diagnostic methods, it was not possible to make a diagnosis of carcinoma of the stomach with reasonable security, and consequently truly radical surgery scarcely ever came into question. Consequently, Albert was but one of the first surgeons to present a long series of successfully executed gastrostomies.

The legacy of Billroth came to Carl Gussenbauer in the year 1894. His name has already been mentioned in the development of the technique of stomach resection. He was also the first to treat pancreatic cysts operatively (1884). He is credited with the solution of numerous technical problems, e.g., the creation of the first artificial larynx (1874) with which he enabled one of Billroth's patients to speak again. Following Gussenbauer's suggested plan of operation, Eric Carl Wilhelm Martini (1843-1880) removed a carcinoma of the colon, in 1879, in Hamburg. The patient was alive and well without recurrence eighteen years later.

Julius von Hochenegg (1859-1940) succeeded to Gussenbauer's chair. An unusually able surgeon, it fell to him to perform the first esophagoplasty by the method suggested by Viktor von Hacker (1852-1933). (The operation involved resection of the larynx and the esophagus for carcinoma.) He was also one of the first to perform a radical operation for carcinoma of the gall bladder with liver invasion. Hochenegg developed new operative techniques for tumors of the gall bladder and kidneys, and for appendicitis and other diseases. His chief contribution was the further development of operative techniques for the removal of colonic, particularly rectal, neoplasms. His successor (1937) Wolfgang Denk, born in 1882, is particularly interested in thoracic surgery.

In 1901, the First Surgical Clinic was given to one of the greatest pupils of Billroth, Anton von Eiselsberg (1860-1939). Among von Eiselsberg's many and varied activities were his work in the surgery of the thyroid, his contributions to the knowledge of the endocrines, his pioneer efforts in neurosurgery, and particularly his operations for tumors of the hypophysis. He added many new techniques to the surgery of the gastrointestinal tract. Together with Hochenegg he founded the Unfallstation (Emergency Hospital for Trauma) which has been of great value for the Viennese, and which has served as an example for similar installations elsewhere. Numerous members of the Eiselsberg school are today scattered throughout the world. He was succeeded, in 1932, by his pupil, Egon Ranzi (1875-1939), who concerned himself primarily with diseases of the spleen, uranoplasty, and particularly with the anatomy and surgery of the central and peripheral nervous systems.

Since 1939 I have had the honor of being Director of the First Surgical Clinic.

Book Reviews

Allgemeine Pathologie. Pathologie als Biologie und als Beitrag zur Lehre von Menschen. Ein Lehr- und Lesebuch für Studenten, Aerzte und Biologen. By Prof. Dr. Med. Franz Buchner, Direktor des Ludwig Aschoff-Houses, des Pathologischen Instituts der Universitât Freiburg. Pp. 528, with 424 illustrations. Berlin, 1950. Urban & Schwarzenberg, 32.80 marks. Agents in U. S.: Grune & Stratton, New York.

This is a functional pathology, written by the late Professor Aschoff's distinguished pupil and successor, Professor Buchner of Freiburg. It is not a text on general pathology, but is essentially a series of brief discourses on a number of subjects in which the author has pursued investigations or has been especially interested over a number of years.

The monograph is sensitively written, in fact, in some areas it is quite philosophic in outlook. In the introduction, the author speaks of inquiring into the nature of life, of illness, and of man's behavior. These, he says, will never be fully understood, but the contemplation of these things by the physician will make him better appreciated by the patient.

The book is printed on excellent paper. The illustrations are good. The references are largely German and include citations also to postwar literature. The book can be recommended to students of metabolic diseases as an important group of studies.

Angewandte Und Topographische Anatomie. Ein Lehrbuch für Studierende und Aerzte. By Prof. Dr. G. Töndury, Zürich. Pp. 416, with 369 illustrations. Georg Thieme Stuttgart, 1951. Agents in U. S.: Grune & Stratton, New York. $16.65.

This monograph comes from the pen of Töndury, the Professor of Anatomy at Zürich, Switzerland. Paul Winkler, a student of medicine has prepared 134 illustrations in color from original dissections.

Surgeons and students of anatomy will find this a helpful and delightful book, and a worthy successor to the *Topographic Anatomy* of Corning of Basel which has been the handbook of many a present-day surgeon.

Every surgeon knows that he must have an acquaintance with both descriptive and pictorial anatomy. It is this reviewer's impression that surgeons will find a text like this a more interesting and helpful source of anatomical information than an applied or surgical anatomy written by a surgeon.

Meister Der Chirurgie Und Die Chirurgenschulen im Deutsche Raum. By Prof. Dr. H. Killian, Freiburg, and G. Kramer, Karlsruhe. Pp. 232. Stuttgart, 1951, Georg Thieme, 24.80 German Marks. Agents in U. S.: Grune & Stratton, New York.

This interesting monograph traces the origin of the Schools of Surgery in the German-speaking countries of Europe. Under the caption of each university, the names of the professors who have held the chairs of surgery in the various university surgical clinics are listed chronologically from the earliest records up until the present time. That professors in the German-speaking medical schools are a migratory lot is well documented here. A brief outline of each professor's background of training, together with an enumeration of his major contributions to surgery appears under that university where he did his major work. Since the turn of the century, there have been ten occupants of the Professorship of Surgery at Greifswald and seven at Königsberg. Among these are some of Germany's greatest surgeons. The number of German professors of surgery who trace their intellectual heritage back through Billroth and Bernard von Langenbeck is amazing. One of the strongest lines of descent has been through Langenbeck, Billroth, Mikulicz and Sauerbruch; another through

Billroth and Eiselsberg. Kocher, Enderlen, Payr, Lexer, and Kirschner are a few great surgeons of the past generation who trace their origin back through a miscellany of sources.

This monograph constitutes an important source book on the history of German surgery of the past 100 years. Every earnest student of surgery will want to have an acquaintance with it.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers as space permits.

ANESTHESIA IN GENERAL PRACTICE. By Stuart C. Cullen, M.D., Head of Division of Anesthesiology, Dept. of Surgery, State University of Iowa Hospital, Prof. of Surgery (Anest.), State University of Iowa College of Medicine. Price $4.50. Ed. 3, pp. 292, with 36 illustrations. Chicago, 1951, Year Book Publisher, Inc.

TREATISE ON SURGICAL INFECTIONS. By Frank L. Meleney, Assoc. Prof. of Clinical Surgery, College of Physicians & Surgeons, Columbia University, and Assoc. Visiting Surgeon, Presbyterian Hospital, New York. Price $12.00. Pp. 713, with many illustrations. New York, 1948, Oxford University Press.

UEBER DIE ROENTGENOLOGISCHEN DARSTELLUNGSMOEGLICKKEITEN DES WEIBLICHEN GENITALAPPARATES MIT HILFE VON JODOL UND JODSOL. By Dozent Dr. Med. Habil. J. Erbsloh, Bad Oldesloe. Price DM 16.80. Pp. 74, with 64 illustrations. 1951. Agents in U.S.: Grune & Stratton, New York.

LEITFADEN DER LAPAROSKOPIE UND GASTROSKOPIE. By H. Lalk, Kassel and W. Bruhl, Arolsen, unter Miturikung Dr. Med. W. Burgmann, Bad Godesberg. Price DM 27. Pp. 157, 82 illustrations. Grune & Stratton (U S.A. Agents) New York, 1951.

CAUSALGIA. By Frank H. Mayfield, M.D., Asst. Prof. of Clinical Surgery, College of Medicine, Univ. of Cincinnati, Attending Neurological Surgeon, Bethesda Hospital, Christ Hospital, Deaconess Hospital, Good Samaritan Hospital, St. Francis and Jewish Hospitals, Cincinnati, Ohio. Price $2.25. Pp. 65, few illustrations. Springfield, Ill., 1951. Charles C Thomas, Publisher.

WIEDERHERSTELLUNGSCHIRUIGIE DES GESICHTS. By Prof. Dr. Reinhard Perwitzschky, Dortmund-Asseln, Direktor Der Hals-, Nasen-, Ohrenklinik der Ehemals Deutschen Universitat Breslau. Price DM 34. Pp. 228, with 176 illustrations. Berlin, 1951, Walter de Gruyter & Co.

FRONTAL LOBOTOMY AND AFFECTIVE BEHAVIOR. By John F. Fulton, M.D., Sterling Prof. of History of Medicine, Yale University. Pp. 154, few illustrations. Ed. 1, New York, 1951, W. W. Norton & Company, Inc.

MICRO-ARTERIOGRAPHY. By Alfred E. Barclay, O.B.E., M.D., O.Sc., Late Honorary Radiologist, Muffield Institute for Medical Research, Oxford. Price $6.75. Pp. 102, 46 illustrations. Ed. 1, Springfield, Ill., 1951, Charles C Thomas, Publisher.

THE PUBLIC HEALTH NURSE AND HER PATIENT. By Ruth Gilbert, R.N., Coordinator, Course for Mental Hygiene Consultants and Asst. Prof. of Nursing Educ. Teachers College, Columbia University. Price $3.75. Pp. 347, no illustrations. Ed. 2, Cambridge, Mass., 1951. Harvard University Press.

ATLAS DER PATHOLOGISCHEN ANATOMIE. By Robt. Rossle and Kurt Apitz, Berlin. Price DM 87. Pp. 297, with 564 illustrations. 1951. Agents in U.S.: Grune & Stratton, New York.

ALLGEMEINE UND SPEZIELLE CHIRURGISCHE OPERATIONSLEHRE. By Martin Kirschner, Weiland O. Professor Dir., der Chirwigischen Klinik der Universitat Heidelberg. Pp. 868, many illustrations. Berlin, 1951, Springer-Verlag.

SURGICAL CARE. By Robert Elman, M.D., F.A.C.S., Prof. of Clinical Surgery, Washington University School of Med., Asst. Surgeon, Barnes Hosp., Assoc. Surgeon, St. Louis Children's Hosp. Dir. of Surgical Service, Phillips Hosp., St. Louis, Mo. Pp. 585, few illustrations. New York, Appleton-Century-Crofts, Inc.

Contents—(Continued from front cover)

The Occurrence in Surgical Patients of Severe Hypernatremia Without Exogenous Dehydration. Bernard Zimmermann, M.D., and Esther F. Freier, B.S., Minneapolis, Minn. ---- 373

Carotid Body Tumors. James W. Hendrick, M.D., San Antonio, Texas ---- 385

Autogenous Vein Grafts in Splenorenal Anastomosis. Louis M. Rousselot, M.D., M.S., Med. Sci. D., New York, N. Y. ---- 403

Experimental Studies With Intra-arterial Transfusion. Edward J. Beattie, Jr., M.D., James R. Thistlethwaite, M.D., Brian Blades, M.D., and Orlyn Wood, M.D., Washington, D. C. ---- 411

Spinal Anesthesia. Paul H. Lorhan, M.D., and Wallace Merriam, M.D., Kansas City, Kan. ---- 421

Case Reports

Agenesis of the Right Lung. Louis B. Thomas, M.D., and Edward A. Boyden, Ph.D.(Med. Sc.), Minneapolis, Minn. ---- 429

Intraintestinal Hemorrhage Following Total Pancreatectomy for Carcinoma of the Pancreas. Robert C. Lynch, M.D., and Dennis M. L. Rosenberg, M.B., B.Ch., New Orleans, La. ---- 436

Recent Advances in Surgery

Fibrosarcoma of the Soft Somatic Tissues. George T. Pack, M.D., and Irving M. Ariel, M.D., New York, N. Y. ---- 443

Surgical History

Surgery in Vienna. Prof. Dr. Leopold Schönbauer, Vienna, Austria ---- 479

Book Reviews

Book Reviews ---- 485

Books Received ---- 486

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